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INTERFACIAL PHENOMENA

WITH ESPECIAL REFERENCE TO COLLOIDS AND ENZYMES*

By W. M. Bayliss

(University College, London)

Although much attention is being given at the present time to the phenomena present in homogeneous solutions, and rightly so, it seems that there is need of more work on the mechanism of reactions in heterogeneous systems, and at the same time a clearer recognition of the fact that the majority of physiological processes take their course in such a system. Even when they appear at first sight to follow the relatively simple laws of mass action as applied to the conditions of homogeneous solutions, it must not be left out of sight that in the living organism they occur in the presence of various solid and liquid structures which may or may not have an important effect on their course.

For this reason, I think that considerations of some such cases form the most useful purpose to which I can devote the first of these lectures, which I am enabled to give by the generosity of the Herter Foundation, to whom I wish to express my deep sense of the honour conferred by the invitation and the pleasure it gives me to put my views before so distinguished an assembly. I wish then to call attention to some points in the mechanism of physiological processes which appear to require further and more critical examination. In doing so, I would at the outset make it plain that I have the highest appreciation of the value of the work which has been done and, where it is necessary to criticize it, the criticisms are made with the object of pointing out the

* Lecture I of the Herter Series delivered before The Johns Hopkins University, March 7th, 1922.

risk of supposing that certain phenomena are already adequately explained, when the statement applies only to some aspects of them. Conditions peculiar to special cases are apt to be extended to a whole group of phenomena. This is particularly so when the colloidal state is involved. For example, a certain group of investigators would explain all the properties of this state on a purely chemical, others on a purely physical basis. It is scarcely necessary to remark that we want to know what is the actual state of affairs, and if we find that the physical state as well as the chemical nature of our systems has to be reckoned with, we base our conclusions on foundations liable to crumble away if we omit either of these.

It is no simple matter to define satisfactorily what is to be looked upon as a heterogeneous system. Perhaps it may suffice for our present purpose to say that it is composed of parts which, although in contact, do not mix together. These parts were named "phases" by Willard Gibbs, to whom we owe so much of our knowledge of the factors controlling equilibrium in systems of the kind mentioned. It will be clear that there are interfaces of contact where the phases meet and that the molecules forming these surfaces are exposed to forces which are not identical with those in the interior of the phases. For one thing, the molecules on the surface only are exposed to chemical action, so that the "active mass" is a function of the surface, not of the total mass present.

Some difficulty arises as to the dimensions required to claim the name of "phase." Single molecules, unless of very large size, cannot be possessed of the properties of surface, which imply the existence of a number of atoms joined together. The problem arises as to whether colloidal solutions obey Gibbs' "phase-rule," a point to which we shall return later.

What then are the most striking properties of surfaces as such? They are two, both conferring the possession of energy.

1. Surface tension, when one of the phases is liquid, and the corresponding property when we have only to deal with solids or gases. This phenomenon is due to the mutual attraction of molecules, giving rise to the "internal pressure" of Young and Laplace and to the "cohesive" forces of Matthews.

2. Electrical charge, which may be given in three ways:—

(*a*) By the deposition of ions by adsorption, as investigated by Perrin. For example, ferric hydroxide may have either a positive or a negative charge, according as it is suspended in acid or alkaline media.

(*b*) By electrolytic dissociation of the surface molecules. Thus, silica forms insoluble silicic anions and gives off hydrogen ions. The latter pass into the water, but only so far as electrostatic attraction to the opposite solid ion permits. The particles have thus a negative charge, but are surrounded by a shell of positive ions in the liquid. Such systems have been called "electrolytic colloids" by Hardy; the large composite insoluble particle, consisting of unchanged matter with a layer of ions on the outside, is a "colloidal ion."

(*c*) By electrolytic dissociation of whole molecules, with aggregation of one or other kind of ions resulting therefrom, the aggregated ion having a charge equal to the sum of those of its constituents. This happens in solutions of congo-red, as shown by my own work; in soaps, according to McBain, who regards the colloidal aggregates as consisting of anions, undissociated soap and water in various proportions. To these McBain gives the name "ionic micelle." The work of Sorensen and others shows that proteins behave similarly.

We may now proceed to discuss some special cases. Space forbids any great detail and I must be content with reference to points which seem to need further elucidation and to some in which my own work has played a part.

Turning first to the phenomena of adsorption, about which a variety of opinions still exists. While some have doubtless erred in attempting to reduce all the phenomena included under this head to changes in surface tension, on the other hand, there are facts which cannot be explained on a purely chemical basis. One of these latter was met with by myself. If we mix a dialyzed solution of the free acid of congo-red with colloidal aluminium hydroxide, free from alkali, a blue complex is precipitated which contains both the acid and the base, but not in chemical combination. They combine, however, slowly at room temperature, quickly if heated, to form the salt, which has the characteristic red colour of the congo-red dyes.

The problem concerns the nature of the forces which cause the attachment of one substance to the surface of another, without chemical combination being of necessity involved. The familiar formula of Gibbs, which gives the degree of adsorption in relation to surface tension, is based on thermodynamical theory. Like all such deductions, it can predict in what direction and to what extent a change of energy will occur, but it does not pretend to explain how this happens. In other words, we need in addition the assistance of molecular dynamics, and I think that it is wisest to admit that at present we have no adequate general theory of adsorption. In all probability, the mechanism is of different nature in different cases. While diminution of ordinary mechanical surface tension plays a part in the adsorption of some organic compounds by charcoal, for example, in the case of the congo-red acid and aluminium hydroxide, above mentioned, where we have to deal with electrically charged surfaces of opposite sign, there is no doubt that electrical forces are chiefly responsible. It is beside the point to urge the objection made by Matthews and to

exclude electrical adsorption on the ground that the combination of sodium and chlorine ions to form sodium chloride would be such a case. The fundamental difference is that in adsorption the chemical nature of the substances concerned is unchanged, whereas when ions unite in a true chemical way the properties are greatly altered. I may be allowed here to express a feeling that when chemists claim the numerous cases of association in which no change of properties occurs as being chemical in nature, they run some risk of obscuring the distinctive character of chemical phenomena.

Langmuir's view of adsorption is sometimes stated to be a purely chemical one. Although, in the case of the taking up of ions by the surface of some crystals, it is intelligible that unsatisfied chemical affinities of atoms in the boundary of the space lattice may cause the deposition of other appropriate atoms, it is not so easy to see how a fatty acid is combined with the surface of charcoal or carborundum. Moreover, as Bancroft points out, if adsorbed chlorine is in combination with the surface atoms of charcoal, it is difficult to understand why it is not an easy matter to obtain compounds of chlorine and carbon by direct union. On the other hand, since the carboxyl groups of acids have a greater affinity for water than the hydrocarbon residue has, it is easy to see why, after deposition on a surface, they are arranged with the former groups projecting into the water phase. But why the acids are in greater concentration at the interface than in the body of the solution is not explained hereby. It may further be remarked that Langmuir's view of adsorption implies that an adsorbed layer can never be more than one molecule in thickness. This is doubtless often the case, but there is also evidence that in some instances the amount adsorbed is in excess of that possible in a layer of the dimensions given. It appears as if the attractive forces extended their action somewhat further outwards than to the depth of one molecule. But such cases need careful investigation and whatever the truth may be, it must not be overlooked, as is sometimes done, that surfaces become saturated, sometimes after taking up only a very small amount of material. The well-known formula of Freundlich, indeed, which takes no account of this fact, applies only to a limited region of concentration. The existence of saturation, therefore, is not evidence that any particular case is not one of adsorption. Although it seems to me that Langmuir's view does not account fully for the facts of surface condensation, there is no doubt that, after orientation on the surface, chemical combination with the material of this surface or between different kinds of adsorbed molecules may occur. This is an important point in relation to the action of enzymes. It will be seen that appropriate orientation may facilitate mutual combination, or oppose it. Cases of the latter kind have been described by Van Kruyt.

To return for a moment to the phenomena of electrical adsorption. Michælis and Rona have recently stated that the staining of paper by so-called "basic" dyes, that is, by salts which consist of a colourless acid in combination with a coloured base, is due entirely to chemical combination with salts contained in the paper. Although this statement is accepted by Prof. Matthews in his interesting article in *Physiological Reviews*, it is so directly in opposition to the work which I published some years ago in the *Biochemical Journal* and with experiments which are regularly made in my classes, that it is a matter of astonishment to me how skilful experimenters could have arrived at it. Since the actual facts are of interest in illustration of the phenomena of electrical adsorption, I may give a brief account of them. If filter paper is dyed with an acidic dye, such as congo-red, the purer the paper, the less is the dye adsorbed. On the other hand, with a basic dye, the purer the paper, that is, the smaller the amount of inorganic salt present, the deeper is the colour. A small addition of a neutral salt, even sodium chloride, has a powerful effect in increasing the depth of stain with the acidic dye, of decreasing it with the basic dye. This effect of electrolytes increases greatly with the valency of the cation. The explanation of these results is simple. Paper immersed in water has a negative charge, as shown by Quincke. The acidic dyes, if colloidal, have also negative charges and in any case the coloured anion is negative. Paper and dye are mutually repellent. Or, looked at from the point of view of energetics, if negative dye were deposited on negative paper, the magnitude of the charge would increase, which is contrary to the second law of thermodynamics. If the dye is positive, as the coloured cation of the basic dyes is, then mutual attraction between it and the negative paper occurs. Now suppose that a soluble inorganic cation, such as sodium, with a positive charge, is present. This will be deposited on the paper, partially neutralizing or abolishing its negative charge; the negative dye will be more easily adsorbed, the positive dye less so. There are various other phenomena which confirm this way of interpreting the facts, amongst others, the effect of inert liquids such as alcohol, which, by lowering the dielectric constant, lower the charge on the paper.

We may pass next to one or two problems concerning the large subject of colloids.

In all questions in which these substances play a part we must never forget that we have to deal with suspended particles of comparatively large size and therefore possessing interfaces of contact with the medium in which they are suspended, on which surface action of various kinds may occur.

The proteins are amongst the most important of the colloids. These, as composed of amino-acids, are "amphoteric" in nature, that is, they can combine with either strong acids or bases. At and near a certain small

hydrogen-ion concentration, called the "isoelectric point," they are free from capability of combination with either acid or base. Their physical properties, viscosity, osmotic pressure, electrical conductivity and so on, have minimal values in this region. So far as they owe their charge to electrolytic dissociation of their salts, they have none at the isoelectric point. A difficulty arises here if a charge can be conferred in any other way than by dissociation, say by adsorption of ions. In fact, as shown by Loeb, gelatin at the "isoelectric point" can be given a positive charge by cerium salts. What does the term "isoelectric point" mean here? It is a pure assumption to say that there is a "loose combination" between gelatin and cerium ions as between it and hydrogen-ions. In point of fact, although the term has a fairly definite meaning when used in relation to amphoteric compounds and hydrogen ions, there is a tendency to make it serve in cases where the state of affairs is altogether different. It was first introduced by Hardy in reference to the discharge and precipitation of arsenious sulphide by barium salts. Its application to the hydrogen ion alone is of later date. It must always be stated what ion is meant, since colloids are made isoelectric by various ions.

We have seen already that ions are adsorbed by surfaces and Perrin showed that the negative charge of cellulose could be nearly abolished by $^{M}/_{20}$ hydrochloric acid. Now in the case of proteins as amphoteric electrolytes, the hydrogen-ion concentration needed to make them isoelectric is a function of their relative strengths as acids and bases. If the isoelectric point of cellulose is to be interpreted in the same way, it would imply strongly acid properties. We must take into consideration the adsorption of hydrogen-ions, and the isoelectric point in this case means the concentration needed to abolish the negative charge which cellulose has in water, whatever may be its origin.

More objection must be taken to the use of the term in relation to the red blood corpuscles where the charge is due to the impermeability of the membrane for cations, while being permeable to anions. This will be considered in my next lecture. It is sufficient to point out here that this same property is responsible for the "Hamburger effect" of acids added to blood as increasing the apparent alkali reserve of the plasma.

It is a difficult matter in practice to find evidence of combination of the serum proteins with acid or alkali unless the hydrogen ion concentration is above 10^{-4} or below 10^{-9} respectively. It was suggested by Gustav Mann that uncombined proteins really exist in the form of internal ammonium salts, requiring a fairly high hydrogen or hydroxyl ion concentration to split the ring. But curves expressing the amount of combination with acid and base are very flat about the isoelectric region, so that it is not an easy matter to be certain on this matter. At all events, there is no appreciable combination between the limits named. In a series of experiments which I have made recently, proteins did not appear to behave towards sodium bicarbonate as such strong acids as their dissociation constants would imply. But there is considerable uncertainty as to their actual molecular weight. In the case of gelatin, however, all the acidic groups appear to be much more equally dissociated than is the case with ordinary di- or tri-basic acids.

A property of importance in regard to colloids in general is that it is practically certain that no single molecule or ion is sufficiently large to satisfy the criterion of not diffusing through parchment paper. At the isoelectric point Sorensen has shown that the Donnan equilibrium is unable to explain the low osmotic pressure of egg white and that there must be considerable aggregation. I have already referred to the cases of congo-red and soaps, in which the osmotic pressure in relation to the electrical conductivity is too low to be accounted for otherwise than on the assumption that the anions form aggregates. So that in any case either the undissociated colloid or its ions are aggregated. Now these aggregates must be large enough to possess surface properties, amongst others that of an electric charge of origin other than electrolytic dissociation of the molecules of the colloid themselves. In other words, a purely chemical theory cannot be the whole story, however satisfactorily an explanation of certain facts is afforded.

In many ways, the most interesting and important of colloidal substances met with in the animal organism is hæmoglobin, and the various considerations which have been previously given have their application to it. The investigation is beset with many difficulties and the more work is devoted to it, the more seems to be necessary. I venture to think that at the present time too much attention is being given to the elaboration of details, interpreted on a limited theory, while there is yet uncertainty about many of the fundamental facts. For example, the isoelectric point as regards hydrogen ions is stated to be on the acid side of the reaction of blood, so that the question arises as to how far the preparations used were, wholly or in part, sodium salts. This possibility raises difficulties in deductions from the osmotic pressure measurements of Hüfner, which more recent determinations suggest were high for free hæmoglobin. The question is of moment also in connection with the carriage of carbon dioxide by blood. Bohr stated that the preparations of hæmoglobin on which he determined the carbon dioxide dissociation curve were free from sodium. Again, according to the acidic dissociation constant of hæmoglobin, compared with that of carbonic acid, it would seem in any case that as much as 95 per cent of the available sodium is in combination with carbon dioxide. If this be so, theories of carbon dioxide carriage on the basis of interchange of sodium have little

support. But the actual molecular concentration of the acidic groups is uncertain. Perhaps the most pressing need is a method of preparing uniform samples of hæmoglobin, of known composition.

It will be remembered that the well-known equation of A. V. Hill was first put forward by him simply as a mathematical formula to express the experimental results obtained by Barcroft and his co-workers on the oxygen taken up by hæmoglobin at different pressures. A definite interpretation was soon, however, put upon the two constants. While expressing the greatest appreciation of the valuable collection of facts, experimental and clinical, made under the inspiration of this view, I must confess to an uncomfortable feeling that it may turn out that little more than the facts themselves stand future investigation. For example, in expressing by Hill's formula the oxygen dissociation curve as it is in the blood, it is found that the exponent, *n*, has to be made of a value between 2 and 3. If therefore it expresses the number of molecules taking part in the reaction, or the order of the mass action equation of velocity, it must be that there are a number of reactions of different molecular order in certain relative proportions. Now I am told by a friend who has looked at the problem from the mathematical standpoint that it is not admissible to take the index by itself and find the relative proportions of the various reactions required to make it of the value found (about 2.4). The equations themselves must be summated. This is a tiresome piece of algebra and seem to require the introduction of further constants to give determinate results. Moreover, it is remarkable that no direct evidence of the existence of such small aggregates in definite proportion has yet been obtained.

In respect to the numerous clinical estimations which have been interpreted on the lines of the Barcroft-Hill equation, the recent work of Lovatt Evans has shown that there is a rapid development of lactic acid in shed blood. This arises from the glucose and is prevented by the addition of 0.1 per cent of sodium fluoride. Since the presence of this acid has a marked effect on the dissociation curve of oxy-hæmoglobin, and also on the alkali reserve, some doubt is thrown on results obtained more than fifteen minutes after removal, unless sodium fluoride had been added.

It is a common experience to find that if acidified hæmoglobin solutions are dialyzed, with the object of obtaining freedom from sodium, methæmoglobin is formed with some rapidity. If 1 per cent of boric acid be added, it was found by A. V. Hill that this change is prevented and the hæmoglobin remains normal. Boric acid is a fairly efficient antiseptic against bacteria, but does not prevent the growth of moulds. The whole question of the relation of methæmoglobin to oxyhæmoglobin would repay further investigation, especially in connection with the manner of combination of oxygen. Perhaps the former is the real *oxygen compound*, the latter something of another kind.

The validity of the phase rule as applied to colloids has its interest in the case of hæmoglobin. If it does apply, oxyhæmoglobin does not satisfy the requirements of a chemical compound. But it is to be remembered that Gibbs excluded from his treatment all factors except pressure, volume and concentration. Since surface energy and electrical forces intervene in the case of colloids, the matter is as yet undecided. Experiments might be made with saturated solutions of hæmoglobin in presence of a definite solid phase, say crystals, in which case the phase rule should hold. It is interesting to note that Cohn obtains evidence of a definite slight true solubility in the case of some proteins.

On the whole, it seems to me that the problem of hæmoglobin might be advanced if it were attacked from a quite independent point of view, taking account of possible effects of surface and without prejudice by previous theories. It is remarkable that the more careful the work with this substance, the more inexplicable it appears. As an illustration, I might refer to the recent researches of Adolph and Henderson on the heat of "combination" of oxygen and hæmoglobin, in which values varying from 1500 to 15,000 were given by a method capable of an accuracy of 1 per cent.

A few remarks are next suggested with respect to enzymes. Here there is no doubt about the fact that their action is exerted at their surfaces. The phenomena are indeed particular cases of catalysis in heterogeneous systems. It is easy to show that many enzymes are active in media, such as alcohol of moderate strength, in which they are quite insoluble and can be filtered off. This is especially simple with urease; powdered soy beans can be extracted with 70 per cent alcohol, the filtrate is inactive, while the residue suspended in alcohol of the same strength hydrolyses urea with rapidity.

It is evident also that adsorption of the reacting substances takes place on the surface of the enzyme phase and that a rapid equilibrium, brought about by some agency or other, is reached. Although the view that there is temporary formation of unstable intermediate compounds between the enzyme and the substrate on which it acts is a favourite one, it must be pointed out that the existence of such compounds, other than mere adsorption, has not been demonstrated. Whether close approximation between the reacting molecules is sufficient, as seems to have been the view of Faraday in the case of the combination between oxygen and hydrogen on the surface of platinum and other substances, or whether molecular forces brought into action raise the chemical potential, as suggested by Hardy; or again, whether the increased concentration raises the rate of reaction by mass action, remains as yet undecided. There is some difficulty in accepting the last view, if it be

supposed that the reaction occurs *after* adsorption because the molecules are fixed in position and the effect of mass is of course due to the movement of molecules. It may be, however, that the increase in rate of reaction occurs in the layer of concentrated solution close to the surface immediately before adsorption. The view of Langmuir that the reacting groups are brought into favourable position, for reaction with one another, by appropriate orientation on the surface, has already been mentioned. It must not be overlooked that acceptance of this view excludes the application of mass action formulæ and the existence of intermediate chemical compounds with the enzyme as explaining the phenomena. But these facts by no means put it out of court. With regard to the former, it is sometimes found that reactions in systems known to be heterogeneous obey, for a part of their course, a simple unimolecular formula. But surely this throws very little, if any, light on the nature of the process; it does not prove that it is a simple chemical reaction, any more than the increase of money at compound interest is. In many processes of the most varied kind, the rate of further change is proportional to what is left unchanged.

If the activity of an enzyme is proportional to the amount of the substrate adsorbed on its surface, it follows that if other substances are present which are themselves also adsorbed, a part of the surface is unavailable for the substrate itself and the rate of reaction will be slowed. I have investigated this in the cases of saponin and of amyl alcohol in their retarding effect on the rate of reaction in urease. It is of interest to find that the effect on the enzyme is merely to slow the rate of action, which ultimately results in the same total change. That the explanation as a case of competing adsorption is correct is confirmed by the fact that the effect has a negative temperature coefficient: that is, it is less at higher temperatures, a characteristic of adsorption phenomena.

The regarding of enzymes as being in the colloidal state suggests a way of explaining many of the effects of the addition of foreign substances, of heat and so on. These may change the degree of dispersion. If the particles become larger by aggregation, the active surface of a given mass is decreased and vice versa. Enzymes are usually destroyed by boiling, but sometimes not. It appears from the work of Chick and Martin on proteins that in the coagulation process the particles may sometimes merely stick loosely together and that they can then be redispersed by conferring an electric charge. In other cases, they fuse together to form a large single particle and redispersion is impossible.

Since the effect of an enzyme as catalyst is to accelerate the attainment of the equilibrium position when the reaction is a reversible one, it is clear that its effect may be either of a hydrolytic or synthetic nature according to the conditions present. I have been unable to discover any evidence of the existence of an enzyme only able to effect a synthetic change, although statements of the kind have been made. The direction of the result produced by an enzyme in those cases where the action depends on the addition or removal of the elements of water, and these are the majority, is controlled by the concentration of water in the system. It is evident that in those frequent cases where the living cell exerts alternatively hydrolytic and synthetic action, say in the removal and storage of glycogen in the liver, there must be some mechanism by which the amount of free water can be changed as required. We naturally think of those colloids called emulsoids, whose particles contain different quantities of water according to the nature and concentration of the medium surrounding them. But there is also the possibility of adsorption of water on the surface. Probably both phenomena take place in the process of imbibition, the nature of which is not yet clear.

In connection with the equilibrium reached on the enzyme surface, there is another interesting problem awaiting investigation. If the constituents of a system are not adsorbed in the same proportion in which they exist in the natural equilibrium, it would be expected that the position of equilibrium under the action of surface catalysis would not be the same as the natural one or that produced by acid. In point of fact, certain cases have been reported where a difference of this kind exists, but whether it can be explained by differences of adsorption is unknown. I have been unable to find any change in the ethyl-acetate system on the addition of dried charcoal.

As a further case of adsorption, at all events as it appears to me, the cell-membrane or plasma-membrane may be considered. This is not to be regarded as a fixed permanent structure, but as produced by deposition of cell-constituents which lower surface energy at the interface between protoplasm and surrounding medium. Thus, it changes with cell activity and is in equilibrium with the cell contents as they alter. Thus, there is no difficulty in the membrane becoming permeable in the active state of the cell to substances to which it is impermeable in rest. Moreover, when a fresh protoplasmic surface is produced by mechanical action, a new membrane is naturally deposited on it. This is no doubt why large particles can be taken up in phagocytosis through a membrane which does not permit even sodium chloride in solution to pass. The particles actually break the membrane, which closes again behind them, in the same way as a needle can be passed through a soap film without bursting it, whereas a gas, such as hydrogen, nearly insoluble in the soap solution, only passes with extreme slowness.

It is not unlikely that a process akin to deposition of solid may occur in the surface membrane, similar to

that described by Ramsden with saponin, proteins and other substances. To account for its varying permeability, the structure suggested by the work of Clowes on phase reversal under the action of electrolytes seems to offer possibilities. A system of oil globules suspended in a watery protein solution can be converted into one in which drops of the watery solution are suspended in oil. It will be clear that a substance soluble in water but not in oil would be able to pass through the continuous watery phase of the former, but unable to pass in the latter case, since the only continuous phase is oil.

Finally, a word or two as to protoplasm itself. In its simplest form as in the clear pseudopodia of amœboid cells, it is a liquid colloidal system or "sol." That it is colloidal is shown by the appearance of an immense number of particles under brilliant dark-ground illumination and that it is liquid is shown by the fact that these particles are in Brownian movement. Under certain states of activity, it may become more jelly-like, its viscosity rises and the particles become fixed in a structure of some kind. I propose to refer to this matter again in the next lecture and for the present will merely call attention to the absence of any visible sign of structure whether of the nature of network, foam, or otherwise. The production of such appearances by the action of fixing reagents was thoroughly investigated some time ago by Hardy, whose work has been rather unduly neglected by histologists. This action of fixing reagents is particularly striking in the case of the cell-body of the neurone, where Mott and Marinesco, independently, showed that there are merely granules or particles in Brownian movement in the living state. The Nissl bodies and neuro-fibrils are to be seen only after fixation, although of course the material out of which they are formed must be present in life.

FACTORS WHICH DETERMINE THE CONCENTRATION OF CALCIUM AND OF INORGANIC PHOSPHORUS IN THE BLOOD SERUM OF RATS

By BENJ. KRAMER and JOHN HOWLAND

There have been a number of experiments upon animals, in the past, with diets deficient in calcium. Most of these have been made in an attempt to produce rickets. The chief investigators, in this period, have been Voit,[1] Diblelt,[2] Aron and Sebauer,[3] Stœlzner and Miwa,[4] and Mellanby.[5] The bones of the animals have been examined. In many instances the diet has been carefully controlled so far as the amount of calcium was concerned but, of the authors mentioned above, only Mellanby has paid attention to the other factors, such as the fat, in the diet. Mellanby has reported no determinations upon the blood. Aron and Sebauer fed to a dog a diet containing only .07 per cent calcium which in the light of our studies, assuming that the dog reacts to a deficency of calcium in the diet as does the rat, should have produced a distinct lowering of the calcium in the blood. They found 6.5 mg. Ca per 100 gms. of whole blood, which is within normal limits. The diet, however, contained a large amount of beef fat (6 per cent) which, in the light of present knowledge, may account for the normal calcium concentration of the blood.

Experiments with diets deficient in phosphorus have also been made, chiefly by Schmorl[6] and W. Heubner.[7] Neither reports analyses of the blood or serum. Within the past few years numerous attempts have been made to increase the calcium concentration of the blood by feeding or injecting calcium salts in large amounts. Among the investigators have been Heubner and Rona,[8] Denis and Minot,[9] von Fenyvessy and Freund[10] and Clark.[11] Analyses of the blood and serum for calcium have been made by various methods. The consensus of opinion is that while it is possible to increase the calcium concentration by the injection of large amounts of calcium, this increase is very temporary and there is a strong tendency for the concentration to be maintained within normal limits. The normal calcium concentration cannot be exceeded even when large amounts of calcium are fed.

Injections of solutions of inorganic phosphate have been made and a temporary increase of serum phosphorus demonstrated (Greenwald,[12] Iversen[13]), but there are no experiments, so far as we are aware, to show any permanent influence upon the inorganic phosphate of the blood or serum resulting from the injection or feeding of phosphorus in any form in excess.

We have attempted to study the factors that control the concentration of calcium and inorganic phosphorus in the serum of rats. The experiments of Dr. E. V. McCollum and of Miss Nina Simmonds, in which the various dietary ingredients have been altered one at a time, have enabled us to do this in a satisfactory manner. We are greatly indebted to Dr. McCollum and Miss Simmonds for the opportunity of making these studies and for the great assistance that they have afforded us, as well as for their enthusiastic cooperation.

The animals were fed and housed in the Department of Chemical Hygiene and are the same animals whose bones and tissues have been studied in the collective

investigation of rickets carried on by the Departments of Chemical Hygiene and Pediatrics.

There are two chief types of experiments. (1) Those in which animals were fed continuously upon the same diet, sometimes for a number of generations and (2) those in which the animals, after being on diets that were known to produce definite changes, were subjected to alterations in the shape of additions to the diet or to some physical influence.

In general the diets were made up so as to contain an excess of, or to be deficient in, some biologically important ingredient. To these diets were added various substances whose influence upon the concentration of Ca or P it was desired to study. By feeding several successive generations of animals upon the same diet it was possible to bring out, in some instances, deficiencies which were not readily apparent in the earlier generations. Some diets were so defective as to prevent reproduction. Others did not allow the animals to survive for even a reasonable length of time.

The appearance and behavior of the animals, the morphological changes in their tissues, especially the bones, have been or will be referred to by others. Our interest has been focused chiefly upon the alterations in the concentrations of Ca and inorganic P of the serum of these animals.

In order to establish normal values for the concentrations of Ca and Inorganic P in the serum we have made determinations of these substances on a large number of rats fed upon diets which allow normal growth through at least four generations and maximum longevity. We believe the normal to be for Ca 9.5 and 10.5 and for Inorganic P 7-8.5 mg. per 100 cc. serum.

There were two chief basal diets. The one was composed of wheat 30, maize 20, rice 10, rolled oats 10, peas 10, Navy beans 10, washed casein 10, the other of wheat 33, maize 33, gelatin 15, wheat gluten 15, NaCl 1, $CaCO_3$ 3.* The first diet was deficient in calcium, the second in phosphorus. Each had sufficient anti-xerophthalmic factor but there was not enough fat of good quality to support normal growth. The proteins of each diet were satisfactory. When the additions (usually small) were made to these diets the proportion of some of the ingredients was necessarily somewhat reduced but not enough to disturb essentially the character of the diet.

The additions were designed either to restore to the diet the deficiency of calcium or phosphorus or to test the effect of certain agents, themselves not containing calcium or phosphorus, upon the calcium and inorganic phosphorus concentration of the serum.

The animals were studied in groups. There were control animals for every experiment usually from the same litter. Our results chiefly represent averages, because the animals of one group were sacrificed at the same time and the blood pooled. Occasionally, if the animals were large enough, estimations were made from the serum of one animal and compared with the pooled serum. The blood was obtained by cutting the carotid arteries and jugular veins under complete anesthesia. The blood after collection was centrifuged at once and the serum removed. The serum was not allowed to stand in contact with the clot.

The calcium was determined by the method of Kramer and Tisdall [14] and the inorganic phosphorus by that of Marriott and Hæssler.[15] The methods were frequently controlled by determinations on solutions containing known quantities of the respective element and by analyses of normal serum.

TABLE I.

Serial No.	Diet		Addition	Serum		Generation
	Ca	P		Ca	P	
633	.64	.40	B.F. 5	10.0	8.4	3rd
630	.65	.45	C.L.O. 2	9.8	8.0	1st
694	.05	.45	0	5.6	—	1st
696	.05	.45	0	5.9	—	1st
761	.05	.45	C.L.O. 0	5.5	8.0	1st
639	.18	.45	0	7.5	8.0	2nd
618	1.22	.30	0	10.5	2.4	1st
683	.09	.45	C.L.O. 2	6.8	8.0	3rd
656	.09	.45	C.L.O. 2	8.8	7.0	2nd
684	.13	.45	C.L.O. 2	10.2	7.8	2nd
666	.17	.45	C.L.O. 2	9.0	8.8	2nd
636	.17	.45	C.L.O. 2	9.4	8.0	2nd
635	.21	.45	C.L.O. 2	9.3	8.0	3rd
657	.21	.45	C.L.O. 2	9.1	8.2	4th
634	.25	.45	C.L.O. 2	9.7	8.2	3rd
658	.25	.45	C.L.O. 2	9.7	8.0	3rd
630	.65	.45	C.L.O. 2	9.8	8.0	1st
647	.65	.45	C.L.O. 4	10.5	—	2nd
652	.65	.45	C.L.O. 5	10.0	8.8	2nd
629	.65	.45	C.L.O. 5	9.8	8.2	2nd
651	.65	.45	C.L.O. 5	10.0	8.0	2nd
648	.65	.45	C.L.O. 7	10.2	—	2nd
639	.18	.45	C.L.O. 0	7.5	8.0	2nd
638	.18	.45	C.L.O. 1	9.6	8.0	2nd
707	.09	.42	S.L.O. 3	9.8	8.4	2nd

C.L.O.—Cod-liver oil.
S.L.O.—Shark-liver oil.
B.F.—Butter fat.
Figures for Ca and P in diet expressed as gms. per 100 gms. of diet.
Ca and P in serum expressed as mgs. per 100 c.c. of serum.

In the second and third columns of the table are given the amounts of calcium and phosphorus in 100 gms. of the diet; in other words, the percentage composition as regards these ingredients. Column 4 states the nature and amounts of the substances added to the basal diet. In the fifth and sixth columns are given the concentrations of the calcium and inorganic phosphorus expressed in the terms of milligrams per 100 cc. of serum.

It will be seen that if the diet contains calcium about .6 per cent and phosphorus .4 - .5 per cent, and if the ani-

* These figures represent gms. per 100 gms. of diet.

mal receives butter fat 5 per cent or cod-liver oil, 2 per cent, normal values for Ca and inorganic P are obtained in the serum even for several generations. If the phosphorus is maintained at the same level but the calcium reduced to .05 per cent, and if no fat is added, there is a marked decrease in the calcium of the serum, the phosphorus remaining normal. An increase in the calcium of the diet raises the calcium of the serum even without the addition of any organic factor.

A most striking effect upon the calcium results from cod-liver oil administration. Even with so low a calcium intake as .09%, cod-liver oil, 2 per cent, added to the diet, raises the calcium of the serum to 8.8 in the second and to 6.8 in the third generation. Such a diet permits reproduction for at least two generations. As the calcium intake rises there is, in general, an increase in the calcium of the serum and when the diet contains only 0.21% calcium, the calcium of the serum is maintained at a nearly normal level for four generations. When the calcium of the diet reaches a certain concentration the addition of more calcium, with or without cod-liver oil, even in large amount does not further raise the calcium in the serum. This is shown in Table I and also in other tables. Determinations 639 and 638 in Table I illustrate several facts. A diet slightly deficient in calcium, containing no added fat but a normal phosphorus concentration, can bring about reproduction at least of one generation. That the diet is defective is indicated by its inability to maintain a normal calcium concentration. When to this diet so little as 1 per cent cod-liver oil is added a normal calcium concentration of the serum is found even in the second generation.

Determination 707 shows that shark's-liver oil is also very effective in maintaining a normal calcium content in the serum despite a low calcium content of the food.

TABLE II.

Serial No.	Diet		Addition	Serum		Generation
	Ca	P		Ca	P	
761	.05	.45	0	5.5	8.0	1st
708	.05	.45	C.L.O. 2% for 6 days	6.5	8.0	1st
762	.05	.45	C.L.O. 2 for 14 days	8.2	7.0	1st

Table II shows the influence of cod-liver oil upon the calcium concentration of the serum of animals receiving very small amounts of calcium. The animals were placed upon the diet without cod-liver oil when about twenty-five days old. They had been on the diet twenty-one days when the oil was added. No 761 represents the control animals of the same age. Cod-liver oil shows its influence in six days and in fourteen days the calcium of the serum has reached nearly normal limits.

A number of facts are illustrated in Table III.

TABLE III.

Serial No.	Diet		Addition	Serum		Generation
	Ca	P		Ca	P	
649	.05	.45	C.L.O. 3	9.7	—	2nd
650	.05	.45	C.L.O. 3	6.1	—	3rd
664	.13	.45	B.F. 8	4.4	8.0	3rd
624	.25	.45	B.F. 3	10.0	8.0	3rd
627	.21	.45	B.F. 8	9.4	8.0	4th
684	.13	.45	C.L.O. 2	10.2	7.8	2nd
656	.09	.45	C.L.O. 2	8.8	7.0	2nd
683	.09	.45	C.L.O. 2	6.8	8.0	3rd
635	.21	.45	C.L.O. 2	9.3	8.0	3rd
657	.21	.45	C.L.O. 2	9.1	8.2	4th

Determinations 649 and 650, 656 and 683 show the influence of generations. In both sets the phosphorus of the diet was adequate; the calcium was very low. Cod-liver oil was added to the diet. This was effective in maintaining the calcium of the serum at a normal or nearly normal level in the second generation but was unable to accomplish this in the third. Determinations 635 and 657 show that when the calcium of the diet reaches about .2 per cent and cod-liver oil is given, the calcium is maintained at a normal level even throughout the fourth generation. Determinations 664 and 627 show that a very slight increase of calcium has a profound influence on the calcium of the serum so that, when the calcium of the diet is increased only .08 per cent, the amount of butter in the diet remaining the same, the calcium concentration of the serum is maintained at a normal level even in the fourth generation, while without this increase the calcium concentration is less than half the normal even in the third generation. When the calcium of the diet is increased to .25 per cent, the calcium of the serum is maintained at a normal level in the third generation in spite of a reduction of butter fat to 3 per cent.

That cod-liver oil has a far greater effect upon the calcium of the serum than butter fat is shown by Nos. 650 and 664. In spite of the fact that one diet contains .08 per cent more calcium than the other and 8 per cent butter fat, the diet with 3 per cent cod-liver oil maintains the calcium of the serum at a much higher level than does the diet containing butter fat.

All the animals represented in Table IV were fed on a diet high in calcium, low in phosphorus and containing just enough anti-xerophthalmic substance to protect the eyes. The animals were placed on the diet at about forty days of age. At this time they usually weighed about 50 grams. They were fed on the diet for from twenty-five to forty days depending upon the condition of the animal. At the end of this time some of the control animals were sacrificed. To the diet of others, substances were added whose influence it was desired to investigate. A few animals were given water but no food for a period of three days and were then sacrificed.

TABLE IV.

Serial No.	Diet		Addition	Serum		Generation
	Ca	P		Ca	P	
618	1.22	.3	0	10.5	2.4	1st
660	1.22	.3	0	10.0	2.8	1st
749	1.22	.3	0	9.8	2.8	1st
675	1.22	.3	0	—	3.0	1st
822	1.22	.3	0	10.2	2.0	1st
668	1.22	.3	C.L.O. 2% 5 days	10.3	5.7	1st
736	1.22	.3	B.O. 2% 6 days	—	3.8	1st
745	1.22	.3	B.O. 2% 10 days	—	4.5	1st
768	1.22	.3	S.L.O. 2% 10 days	—	6.0	1st
769	1.22	.3	M.O. 20% 15 days	10.1	2.7	1st
770	1.22		O.O. 20% 15 days	9.9	2.4	1st
653	1.22	.3	B.F. 30% 10 days	10.2	4.4	1st
640	1.22	.3	B.F. 30% 14 days	—	7.0	1st
673	1.22	.3	B.F. 15% 12 days	—	4.8	1st
803	1.22	.27	0	9.4	2.0	1st
807	1.22	.32	0	10.0	2.0	1st
808	1.22	.30	0	—	2.6	1st
809	1.5	.3	—	10.0	1.8	—
674	1.22	.3	Starvation 3 days	—	8.6	—

B.O.—Burbot-liver oil.
M.O.—Maize oil.
O.O.—Olive oil.

Upon this basal diet, with great uniformity, the calcium concentration of serum is maintained at a normal level, while the inorganic phosphorus varies between 2 and 3 milligrams. First generation animals alone are included in the table because reproduction upon this diet is impossible.

All the fish-liver oils employed and these include those from the cod, shark, and burbot (freshwater) raise the inorganic P concentration of the serum. This effect is the more pronounced the longer the period of administration. The fact that normal figures were not reached was probably due to the short period of administration. The vegetable oils (maize and olive), even when administered in large amount, have no demonstrable effect. Butter fat occupies an intermediary position between the liver and vegetable oils. It has a distinct effect upon the phosphorus but it must be offered in larger amounts and for a considerable period of time.

When food is withheld for three days a rapid and remarkable increase of the inorganic phosphorus takes place. The inorganic phosphorus concentration of the serum rapidly reaches the normal level.

TABLE V.

Serial No.	Diet		Addition	Serum		Generation	Radiations from
	Ca	P		Ca	P		
749	1.22	.3	0	9.8	2.8	1st	
663	1.22	.3	0	10.3	3.5	1st	U. V. Ferric chromium condenser spark.
646	1.22	.3	0	—	4.5	1st	U. V. Ferric chromium spark.
662	1.22	.3	0	10.2	5.4	1st	U. V. Cadmium spark.
669	1.22	.3	0	10.2	5.7	1st	U. V. Cadmium spark.
671	1.22	.3	0	—	2.7	1st	Cadmium spark filtered through glass.
716	1.22	.3	0	10.4	4.1	1st	U. V. Mercury vapor quartz lamp.
733	1.22	.3	0	9.6	3.2	1st	Ozone.

Table V shows the effect of certain physical agents upon the inorganic phosphorus of the serum. The diet was the same as that given to the animals represented in Table IV, *i.e.*, one which contained an excess of calcium and a deficit of P, so that while the calcium of the serum was at a normal level the inorganic phosphorus of the serum was invariably low. The animals were given the basal diet, beginning at about four weeks of age, for a period of twenty-three to thirty-eight days.

They were then exposed to radiations emanating from various sources. Spectroscopic analysis of the rays was made in each instance to determine the presence or absence of the ultra-violet. The mercury vapor quartz lamp yielded rays which gave, among others, a band in the region of the second ultra-violet. A similar but more intense band was obtained with the cadmium spark. The inter-position of a plain glass filter blocked the second ultra-violet rays while it allowed the passage of a part of the first ultra-violet. The ferric chromium condenser spark gives rays which are rich in the first ultra-violet but poor in the second ultra-violet.

It will be seen from the table that following radiation by the mercury vapor quartz lamp, by the cadmium spark and by the ferric chromium condenser spark there is a definite increase in the inorganic phosphorus of the serum. The only exception is when the rays are filtered through glass. Following this there is no demonstrable effect. The rays from the ferric chromium condenser spark are the least, those from the cadmium spark the most effective; those from the mercury vapor quartz lamp occupy an intermediate position. In all of these tests the time of exposure varied from fifteen to thirty minutes. The animals received ten treatments. The distance from the source of light was six inches. As there is a rapid formation of ozone by the mercury vapor quartz lamp a group of animals have been exposed to ozone for the same period and frequency as when radiations were employed. One of the animals had refused food for several days. The slight increase of inorganic phosphorus was probably the result of pooling the serum

of this starving animal with that of the others. The increase over that from the basal diet in any event was not significant.

TABLE VI.

Serial No.	Diet		Addition	Serum		Generation
	Ca	P		Ca	P	
749	1.22	.3	0	9.8	2.8	1st
782	1.22	.47	Cas. 20% for 10 days	10.4	4.4	1st
681	1.22	1.21	$CaH\ PO_4$ 4% for 10 days	5.0	7.2	1st
842	.05	.45	0	4.4	8.0	1st
846	.05	.56	$NaH_2\ PO_4$ .425%	4.5	7.2	1st
843	.05	.66	$NaH_2\ PO_4$ .85%	4.5	—	1st
847	.05	.87	$NaH_2\ PO_4$ 1.7%	—	8.0	1st
841	.05	.95	$NaH_2\ PO_4$ 2.1.%	4.2	—	1st
844	.05	1.06	$NaH_2\ PO_4$ 2.5%	4.1	8.6	1st

In Table VI are shown results obtained with animals fed upon both types of basal diets. The diet of some animals was high in calcium and low in phosphorus. The phosphorus was increased by the addition of casein or of secondary calcium phosphate. Both of these substances raised the inorganic phosphorus of the serum, but whereas the casein had no effect upon the calcium, the secondary calcium phosphate reduced this by fifty per cent, in spite of the large amount of calcium in the diet.

The second diet was very low in calcium and contained an adequate amount of phosphorus. The control animals on this diet have regularly from 4 to 5 mgms. of calcium with a normal phosphorus concentration in the serum. The addition of acid sodium phosphate to this diet in increasing quantity produced practically no effect upon the concentration of calcium or phosphorus. There was a slight tendency for the calcium to diminish and the phosphorus to increase in the serum with the larger additions.

SUMMARY

A study has been made of the influence of various factors upon the concentration of calcium and inorganic phosphorus in the serum of rats. The concentration of neither element has been distinctly increased beyond normal limits, either as the result of various additions to the diet or the use of physical agents. It seems fair to assume that this cannot be done by either of these methods. On the other hand, it is possible to reduce the concentration of these elements in the serum by feeding diets containing an insufficient quantity of the respective elements.

In order to bring this about there must be only enough of the organic factor represented by cod-liver oil or butter fat to prevent xerophthalmia and allow moderate growth. Even with a very small amount of calcium or phosphorus in the diet, compensation occurs and the concentration of these elements in the serum approaches the normal level if sufficient of the organic factor is included in the diet. A defect in the diet is accentuated in succeeding generations, so that a diet which gives a normal value for the serum calcium in the second generation may give a distinctly low figure in the third generation. Of the fats that have been employed in these experiments the fat from the livers of fish has been much more effective than butter fat. The vegetable oils (olive and maize) have been without influence.

When the concentration of either element in the serum is low as a result of a deficiency in the diet, it may be increased by increasing the amount of the respective element in the food. Up to a certain point even small additions to the diet have a pronounced effect upon the serum. Further additions have no effect whatever if a normal concentration has been reached.

When the diet is defective in phosphorus and the phosphorus of the serum is therefore low, a marked increase of the serum phosphorus may be produced by starvation, by the addition of phosphorus to the diet in organic or inorganic form, by various fats, and by exposure to radiations from various sources which yield, among others, rays whose wave lengths are less than 3000 Aengstrom units.

The relation of these findings to rickets and to calcification in general will be discussed in a subsequent communication.

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A STUDY OF THE RESULTS OBTAINED IN SIXTY-FOUR CAESAREAN SECTIONS TERMINATED BY SUPRAVAGINAL HYSTERECTOMY

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Eardley Holland [1] has recently published a statistical study of 4197 Cæsarean sections which were done in Great Britain during the decade from 1911 to 1920, and which in a way formed a continuation of a similar study by Armand Routh [2] for the previous decade. He stated that in the series there were forty-six Cæsarean sections which had been terminated by supravaginal hysterectomy with eight deaths, a percentage of 17.4. As this is far in excess of the mortality in our service, it seemed that it might be interesting to study the results which we have obtained and to compare them with those reported by Holland.

From the early days of our service it was noted that the convalescence following supravaginal amputation was more satisfactory and much smoother than that following most conservative sections, with the result that we gradually came to employ the former operation whenever it seemed justifiable, more particularly in two classes of cases;—First, as the method of choice for effecting sterilization after repeated Cæsarean section, and secondly, as a means of obtaining more ideal results upon patients who were already infected or who were admitted to the service after being long in labor.

In the earlier days of the service many conservative Cæsarean sections were done in the second stage or late in the first stage, with the idea that the patient should be given a test of labor in order to ascertain whether the head would or would not engage. We gradually learned that this was an erroneous practice and resulted in a relatively high mortality. After this we limited the performance of conservative Cæsarean section practically to such patients as could be operated upon at an appointed time before the onset of labor or as soon as possible after the appearance of labor pains; while in patients who were seen late in labor or who already presented signs of infection, we either did not do a Cæsarean at all or removed the uterus after its performance. Some idea of the improvement of the results which followed may be gained from the fact that in the first fifty Cæsarean sections done in the service the mortality was twelve per cent, while in the following 173 operations done up to May 15, 1922 it became reduced to 2.88 per cent.

In 223 Cæsarean sections which have been done in the obstetrical service of the Johns Hopkins Hospital up to May 15, 1922 the uterus was removed by supravaginal hysterectomy in 64 instances. For purposes of study we have divided our 64 cases into two main groups—the first including all patients from whom the uterus was removed at the first Cæsarean section, and the second those from whom it was removed at the second or third section, as shown in Tables 1 and 2. The indications, which were discussed in detail in Dr. Williams' paper "A Critical Analysis of Twenty-one Years' Experience with Cæsarean Section,"[3] covered our material up to the end of 1921.

TABLE I.
Supravaginal Hysterectomy at First Cæsarean Section.

Late in Labor or Manifest Infection	10
Sterilization	5
Heart Disease	5
Atresia of Cervix	5
Neglected Transverse Presentation	4
Myoma of Cervix	3
Hour-glass Contraction of Uterus	2
Apoplexy of Uterus	2
Failure of Bag or Bougie	2
Uncontrollable Hæmorrhage	2
Dystocia following Ventral Fixation	1
Total	41

TABLE II.
Supravaginal Hysterectomy at Repeated Cæsarean Section.

Late in Labor or Manifest Infection	8
Sterilization	13
Tearing of Uterine Incision	1
Blocking of Outlet by Condyloma	1
Total	23

Our figures show that in the sixty-four patients there were three deaths, a gross mortality of 4.68 per cent, which is, roughly speaking, only one quarter as great as that reported by Holland. As will be seen below, none of the deaths were due to infection and only one of them was associated directly with the operation. The latter occurred at a second section upon a multiparous patient with a generally contracted pelvis, from whom the uterus was removed for the purpose of effecting sterilization. Owing to the inexperience of the operator difficulty was experienced in ligating the left uterine artery, with the result that death from hæmorrhage occurred on the operating table.

The other two deaths were not connected with the operation and occurred under the following circumstances. The first was in a seventeen-year-old primipara,

who came into the service on account of acute ulcerative endocarditis with broken compensation. As she was steadily growing worse, and as it was felt that the abdominal enlargement was aggravating her condition, it was decided to empty the uterus. It appeared that this could be accomplished most conservatively by Cæsarean section, and as it was furthermore felt that future pregnancies should be avoided, the uterus was removed by supravaginal hysterectomy. Death occurred on the eighth day from the cardiac condition. At autopsy no sign of wound infection was present, but an acute thrombo-endocarditis with perforation of the aortic valves was found.

The second patient was a multipara who had been under treatment for several months for hypertension not associated with albuminuria. At the eighth lunar month she began to bleed as the result of premature separation of the normally implanted placenta. A Vorhees bag was introduced which controlled the bleeding, but failed to dilate the cervix. Ten hours later the patient became alarmingly worse with rapidly increasing stupor, marked increase in the blood pressure and the presence of fifteen grams of albumin per liter in the urine, from which it previously had been absent. Under the circumstances it was felt that the only chance for recovery lay in immediate delivery and that this could be accomplished most satisfactorily by Cæsarean section. Upon incising the uterus we found the placenta completely separated and lying free in the uterine cavity, which contained several hundred cubic centimeters of blood. Hæmorrhage had also occurred into the walls of the uterus and had led to such disassociation of its muscular fibers that contraction could not occur. As the organ remained soft and flabby in spite of the administration of pituitary extract and manual irritation, supravaginal hysterectomy was done. The patient died in coma shortly after its completion. Although an autopsy could not be obtained, it was apparent that death had not occurred from hæmorrhage, as the total amount of blood lost, including that retained in the uterine cavity, did not exceed six hundred cubic centimeters. In the circumstances, therefore, it seems justifiable to attribute the death to the pre existing renal condition, which had become accentuated by the premature separation of the placenta.

These three deaths represent a mortality of 4.68 per cent, but, as has been indicated, only 1.56 per cent could in any way be attributed to the operation. Such results are far superior to those reported by Holland and it might be interesting, but in view of the absence of sufficient data it would be useless, to speculate as to the cause of the deaths in his series. In any event, our figures indicate that those of Holland give a distorted picture of the dangers following supravaginal hysterectomy, and indicate that the results obtained in our hands are essentially as satisfactory as in elective conservative sections done at an appointed time before the onset of labor or within the few hours following the appearance of uterine contractions. This is particularly emphasized when we consider that in a considerable portion of our cases the condition of the patient when first seen was such as to suggest that infection had already occurred.

In this connection it is interesting to ascertain whether we have unnecessarily sacrificed the uterus and thereby ended the reproductive career of our patients. This can be answered only by studying our cases in somewhat closer detail, and the verdict will depend in great part upon one's point of view. As is evident from Tables 1 and 2, the uterus was removed from eighteen patients solely for the purpose of effecting sterilization. Five of such operations were done at the first and thirteen at a subsequent section.

Whether the removal of the uterus in such cases was indicated depends altogether upon one's point of view; first, concerning the justifiability of sterilization in general, and secondly, upon whether it can best be accomplished by removing the uterus. We have always taken the view that hopelessly deformed or mentally defective patients from the lower classes should be sterilized, and, furthermore, we have made it a rule to sterilize all patients at the third section, considering that in such circumstances the woman had done her duty by society. Accepting such an indication for sterilization, it must be admitted that it can be effected in one of two ways, either by doubly ligating the tubes and burying the proximal ends between the folds of the broad ligaments, or by removing the uterus. If the patient is intelligent, this decision is, in great part, left to her and she is asked whether or not she desires to menstruate after the operation. If she replies in the affirmative, the tubes are ligated, but if in the negative, the uterus is amputated as the easiest and most satisfactory method of attaining the desired end. In addition to these eighteen cases, the uterus was removed from five other women suffering with serious heart disease, as it was felt that in their cases sterilization should follow the first Cæsarean.

Thus we have twenty-three patients in whom the prime or secondary object of the hysterectomy was sterilization, leaving forty-one on whom it was performed for other indications. Eighteen of these were done frankly on account of the patient coming into the service already infected or late in labor. In addition to these, the uterus was removed on account of atresia of the cervix in five instances, neglected transverse presentation in four instances, hour-glass contraction of the uterus in two instances, failure of the bag or bougie to bring about labor in two other instances and dystocia following ventral fixation of the uterus in one instance—a total of thirty-two cases. With the exception of the cases of atresia of the cervix, all of these thirty-two patients were operated upon late in labor and after they had been examined frequently by the vagina, and sometimes sub-

jected to unsuccessful attempts at delivery by other methods. In several of the cases of atresia of the cervix the patient had a high temperature at the time of admission, and it was felt that a satisfactory result could be obtained only by the removal of the organ. Adding these cases to those in which sterilization was the prime indication, we find that they aggregate fifty-five in number, leaving nine others in which the operation was done for some other cause.

The justification for removing the uterus in the former group of cases lies in two considerations; first, the only death which occurred was an operative accident, as compared with the 9.4 and 26.5 per cent mortality following conservative Cæsarean section performed late in labor or after attempts at delivery, as shown by Holland's statistics. Furthermore, as shown in Table 3, sixty of the uteri amputated were subjected to histological study and in twenty-three of them definite histological evidence of ascending infection was found in the shape of leucocytic infiltration or actual inflammatory reaction in the mucosa of the cervix and lower uterine segment. Moreover, in many specimens the presence of bacteria could be demonstrated by suitable bacterial stains. On the other hand, in the twenty-seven patients from whom the uterus was amputated at an appointed time at the end of pregnancy or within six hours after the onset of labor, signs of infection were present in only one, whereas in the twenty-eight patients who were operated upon late in the first stage or during the second stage of labor eighteen presented histological evidence of infection.

TABLE III.
Histological Study of Amputated Uteri.

Duration of Labor	Total Specimens	Inflammatory Changes	Percentage
Before or within 6 h. of Onset	27	1	3.7
6 to 18 hours	5	4	80.0
Late 1st or 2nd Stage	28	18	64.3
Total	60	23	38.3

While it is not our intention to contend that all patients with ascending infection would necessarily do badly, it does, however, seem to us that many of them would have done so, and, accordingly, we feel that we have adduced a satisfactory scientific justification for our course of procedure. Moreover, we feel confident that, had the conservative operation been done, or even one of the various types of extra-peritoneal, low cervical or flap operations employed, many more of our patients would have died and we should have had results comparable to those obtained in the first fifty cases of our series, as well as with the figures given by Reynolds,[4] Routh,[2] and Holland [1] in late operations.

This being the case, we do not feel that we have unnecessarily sacrificed the uterus, but, on the contrary, we are convinced that our procedure has resulted in saving the lives of a considerable number of women who would otherwise have died.

It is generally believed that premature rupture of the membranes adds materially to the danger of operation, in that it favors ascending infection. In general this is doubtless true, but our material serves to show that ascending infection may be present without its occurrence, as on examination of the history of the patients, in whose uteri histological evidence of ascending infection was present, it was found that the membranes were intact in nine. On the other hand, in the eleven patients from whom the uterus was removed after labor had been in progress for six hours or more and in which histological examination showed the absence of ascending infection, it was found that the membranes had ruptured in seven and were intact in four instances. While such figures clearly indicate that premature rupture of the membranes does increase the danger of infection, they likewise indicate that the main factor concerned is the actual length of labor, and that whenever it has lasted for more than six hours the probability of ascending infection must always be considered and will increase with every additional hour the labor has lasted.

Furthermore, it is generally admitted that a temperature of 100.4° F. or more during labor raises the presumption of intra-partum infection. Upon studying our material with this in mind, we find that nine of the sixty-four patients presented elevations of the intra-partum temperature. The uterus from five of these presented signs of ascending infection, while in the other four it did not. To put it in another way, it might be stated that, in the twenty-three uteri which presented histological evidence of ascending infection, the condition was preceded by intra-partum fever in only five instances. In other words, the infection was preceded by elevation of temperature only in five out of twenty-three instances. Accordingly, we may conclude that, while the occurrence of intra-partum fever raises the presumption of ascending infection, its absence by no means indicates that it has not already occurred. Here again we must draw a conclusion similar to that in connection with premature rupture of the membranes; namely, that the great danger arises from the prolongation of labor rather than from any of the factors upon whose occurrence we have in the past laid such weight.

For these reasons we have come to regard the late Cæsarean as an extraordinarily dangerous operation and, in such cases, if we are not prepared to sacrifice the uterus, we must resort to pubiotomy or the destruction of the child if we wish to safeguard the patient, whereas, if we resort to radical measures, we may obtain results comparable to those following conservative Cæsarean section done at an elective time either before or just after the onset of labor.

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AIR EMBOLISM FOLLOWING VARIOUS DIAGNOSTIC OR THERAPEUTIC PROCEDURES IN DISEASES OF THE PLEURA AND THE LUNG

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Probably it would not occur to any physician to suggest that air emboli following such common technical procedures as puncture to clear up the nature of an effusion in the thoracic cavity, or irrigation of a long-standing empyema cavity with an antiseptic solution such as bichloride of mercury, hydrogen peroxide, or Dakin's solution, or change of position of the tube draining such a cavity, may cause complications that could endanger the life of the patient. Roger,[1] a French physician, in 1864 first called attention to these accidents in his observation on a child eight and a half years of age suffering from a chronic empyema cavity. While the customary irrigation of this cavity with an antiseptic solution, with the use, perhaps, of a flow stronger than during the other irrigations, was being performed, the child fell backward from her sitting position, unconscious. She showed clonic contractions of both upper and lower extremities, similar to those of epilepsy. This attack lasted one hour. The child lay drowsy for the rest of the day. By the next day all the symptoms were gone, and she felt normal. Basing their opinion on this incident and others similar to it, Roger, and later on other French physicians, Besnier,[2] Legroux,[3] and Lépine,[4] concluded that these attacks were of nervous origin—an irritation of sensitive nerve fibres in the pleura, which transmitted this irritation to the central nervous system. They spoke of this reaction as a *pleural eclampsia* or *pleural epilepsy.*

These first clinical experiences were gained from accidents following irrigation of an old empyema cavity, as in Roger's case, or from diagnostic puncture of the chest wall for a supposed circumscribed abscess formation. For a long time irrigation was carried out without any complications. Then, in one case the patient fell unconscious; in many instances there was an aura at the onset. Sometimes the patient complained of visual disturbances, and at the same time had a prickling pain in the discharging side. Headache and dizziness at times accompanied the onset. These initial signs were followed by clonic or tonic contractions of one limb; or all the limbs were involved. The two forms sometimes alternated. Even the facial nerve was affected. These motor troubles were accompanied by eye symptoms,—dilated pupils on the affected side, on the opposite side, or on both sides. Respiration ceased or became of the Cheyne-Stokes type. At the same time there was also abnormality of the heart action, the pulse becoming accelerated and very thready. At this stage the unconscious patient often had involuntary movements of the bowels. If a sudden change in the clinical picture did not take place, death terminated these so-called pleural eclampsies. At autopsy there were very often no positive findings.

In cases where the patient recovered after several hours or even after some days, a paralysis very often persisted for a time, generally in the muscles which had been most affected by the motor disturbances. St. Philippe[5] observed a left-sided palsy in a case of left-sided empyema. No general rule can be made out about the relationship. In Walcher's[6] case the paralysis lasted for two days. The average duration was from a fraction of an hour to several hours. Aphasia of short duration was an exceptional symptom after these pleuro-pulmonary complications. Blindness was the most impressive sign noticed by the patient at the onset of the attack. It lasted for some hours or for days. During an attack the pupils were generally dilated, not reacting, and often unequal. Marble-like discoloration of circumscribed spots of the skin, as the forearm, or calf, was noticed in a few cases. The great variety in the clinical symptoms in these attacks is striking. The negative findings at autopsy strengthened Roger's opinion as to the nervous etiology of these complications.

Raynaud[7] in 1875 also supported this belief in the origin of these pleural reflexes, as did Bouveret,[8] Brouardel,[9] de Cérenville,[10] Desplats,[11] Dumontpallier,[12] Gilbert,[13], and Letulle.[14] Cordier[15] and Gilbert tried to verify their opinion by experiments on animals. In Da Costa's Modern Surgery[16] Dr. Toland is quoted as hav-

ing observed four cases of pleuritic epilepsy following irrigation with Dakin's fluid. Da Costa refers to Quénu as having seen intense dyspnœa, great shock, disturbances of respiration and circulation, convulsions, and death follow injections of the blandest fluid (de Cérenville: pleural epilepsy).

Similar accidents were observed after the performance of other therapeutic procedures, such as introduction of a probe or a rubber catheter into a narrow sinus of an old empyema cavity. In cases in which the canal had to be dilated by a laminaria stick, these reflexes also occurred. It is interesting to note that in all these cases with complications there was bleeding from the cavity, showing that a mechanical lesion of the fibrous wall of the canal or of its granulating surface had occurred.

Brandes [17] published the report of a case in which he tried to outline the extent of an empyema cavity by an injection of bismuth paste through the sinus. The rubber catheter apparently injured the wall of the cavity. Most of the bismuth escaped alongside of the catheter. The patient had a spasm, with deviation of the eyes, and died after 20 hours. At autopsy, bismuth was found in the smallest blood vessels of the cerebral cortex of both hemispheres. On examination of serial sections from the wall of the sinus, the bismuth could be traced up to the pulmonary capillaries and veins. The catheter had injured the granulations and opened some venules underneath. Bismuth was also found in other capillaries of the greater circulation.

Puncture of the pleural cavity is quite a common procedure, familiar to every practitioner. For example, in the course of a pneumonia we suspect an exudate in the affected pleural cavity, and perform a puncture to clear up the diagnosis. Or the clinical findings and the X-rays make it very likely that we have to do with an interlobar empyema or a lung abscess; the diagnosis is made certain by the puncture. A clinical picture similar to that given above may be encountered when carrying out any of these procedures. Two striking cases may illustrate the truth of this statement.

Jessen [18] was giving local anæsthesia to a patient thirty years of age with tuberculosis of the lung for a thoracoplasty over a tuberculous cavity, and was trying to make a special deposit of the fluid on the pleural side of the rib. At this moment the patient had an attack of coughing, and fell unconscious, with partial pallor, cyanosis, and clonic twitchings of the left arm. Blood-stained sputum was observed. Respiration and heart action were at first normal. Later on the reflexes were found to be absent. The pupils became narrow, and did not react. The patient died 16 hours after the onset of the attack. The autopsy showed a puncture wound in the indurated wall of the tuberculous cavity. The mucus in the bronchi was stained with blood. No air could be found in the vessels of the brain.

A second case, observed in Professor Clairmont's clinic (Zürich), was published by me in the Deutsche Zeitschrift für Chirurgie.[19] A street car conductor, thirty-four years old, had suffered with a recurrence of bronchitis which had developed into broncho-pneumonia. On the supposition of the existence of a circumscribed abscess, the right lung was punctured twice without result and without accident. Relying on the typical clinical picture, the operator repeated the puncture in several places some days later with the same negative result. A week later a new attempt to help the patient was made. The X-rays showed in the right lung a circumscribed area filled with fluid. Resection of a segment of the fourth rib was made under local anæsthesia. Before going further a puncture was made and some bloody fluid was withdrawn into the syringe. For examination of this fluid the syringe was detached, the lumen of the needle being now in free communication with the atmosphere. At the moment the syringe was taken off the patient collapsed. He became unconscious, with fixed pupils, and clonic convulsions (twitchings) of all muscles. Some minutes later he became conscious again. Within two and a half hours he had gradually recovered completely, except for loss of sight. The ophthalmoscopic examination revealed a normal fundus. The blindness lasted for three days. The patient had an increased muco-purulent expectoration. The signs of abscess cleared up without further operation. The patient improved every week, becoming finally normal after six months, when he resumed his occupation.

In these two cases the presence of air embolism seems very probable, but the diagnosis was not confirmed either by the clinical findings (ophthalmoscopic examination) or by autopsy.

The first clinical observations of what proved to be experimental air emboli, unintentionally produced, were made in cases of accident in pneumothoraxtherapy for tuberculosis. The phthiseotherapists frequently employ artificial pneumothorax in cases of unilateral pulmonary tuberculosis. It is especially to Forlanini [20] (1882) that we owe the introduction of this procedure in medicine. He advised the so-called puncture method, in which the needle is introduced directly through the thoracic wall. Accidental puncturing of the lung may occur, and with this there may be trauma of some engorged veins in a tuberculous area underneath the surface of the lung, with sequelæ, which we shall consider later. This grave danger, with subsequent air emboli, led J. B. Murphy [21] to suggest exposure by a preliminary incision of the parietal layer of the pleura, with introduction of the needle into the fissure of the pleural cavity. Brauer [22] became a strong supporter of Murphy. He was the first to recognize, in 1912, the danger of air embolism in thoracic work,

and rejected the opinion held by Roger and others as to these so called pleural reflexes. Wever's [23] experiments are convincing. Forlanini did not admit the possibility of the presence of air emboli. He maintained the old conception of the nervous origin of the convulsions.

Among the phthiseotherapists using pneumothoraxtherapy (Spengler,[24] Saugmann,[25] Giesemann,[26] Sundberg,[27] and v. Voornveld [28]) air embolism as the cause of the fatal outcome during this treatment is generally accepted. Jessen believes that the frequency with which air embolism occurs is much greater than is recognized, and in support of his view is the statement of a colleague of Dr. von Voornveld, that he had given up this therapy because he had had three deaths in 12 cases. Many of the cases are registered as death from chronic myocarditis, cachexia or shock. This evidence shows that prominent physicians in Europe do not agree with the conception about pneumothoraxtherapy of Da Costa, who points out that there is little danger in the method, although possibly trouble may follow. That statement may perhaps hold good when the Murphy-Brauer method with the incision is employed. But in Europe, where the Forlanini-Saugmann puncture technic is generally used, there is some danger that this method, even in the hands of an experienced physician, may cause air emboli, although the technic has been worked out to diminish to a great extent the possibility of danger. The first puncture presents the greatest risk, but in cases of a partial pneumothorax the danger is always present. When the operator is refilling or increasing the air content, the needle may either pass into a strand of adhesion, thereby opening a vein, or may pierce infiltrated lung tissue. The same complication occurs when the strand of adhesion breaks through near its attachment to the lung surface. It is on account of this possibility that the adhesions are cut through near their attachment to the pleura when Jacobaeus'[29] thoracoscopy is employed. Even then the danger is not completely eliminated.

The following figures will give some idea of the frequency with which these complications may occur in the hands of even expert operators. Forlanini [30] had, in 10,000 punctures on 134 patients, 12 accidents, 5 with temporarily serious conditions, but all with final recoveries. In a second report he had in 1454 insufflations on 28 patients 4 complications without a death. Saugmann [31] records 970 operations on 54 patients without complications. In a second series [32] he had in 215 first punctures and 5500 follow-up treatments 2 cases of embolus. Extracts from some histories may illustrate these accidents.

Saugmann [33] tried to introduce air into the chest of a man twenty-two years of age, with unilateral pulmonary tuberculosis, which had existed for some five years. A first session was without result. A wide manometric excursion, corresponding to inspiration and expiration—proof that the needle is in the pleural cavity—was not shown. At a second attempt the oscillations of the manometer were only minimal, and the procedure was given up. Later, a third effort was made with the same result. The patient was then told to take a deep breath. At this moment he turned pale, and complained of dizziness. The needle was taken out. The patient became unconscious, and vomited, and the breathing became very irregular. On the right side the pupil was large; the eyes showed divergent strabismus. The pulse could not be felt. Although various stimulants were employed, the breathing stopped also. The autopsy revealed two prick lesions in caseous pneumonic lung tissue, with some suffusion of blood. No large blood vessel was implicated.

In a second case of Saugmann,[34] a woman, aged thirty-two, with a long-standing left-sided tuberculosis, the patient was very nervous. The inserted needle was connected with the manometer, but the latter did not show any wide excursions. An obstruction in the canal of the needle was supposed to be the cause and a stylet was passed. The patient took a deep breath. The stylet, on being withdrawn, showed some blood. At this moment the patient said that she felt giddy. The needle was suddenly withdrawn. The patient became pale. She lay on her back, unconscious, the eyes and the head turned to the left, with the pupils at first contracted, later dilated. Respiration and the heart's action became irregular; the pulse stopped and death occurred. At autopsy a mechanical lesion made by the needle in the lung tissue was found, with bloody suffusion of the whole area. On microscopic examination the damaged vein could be seen. In the vessels at the base of the brain, especially in the Sylvian artery, gas bubbles were found.

Spengler [35] cites the case of a girl, eighteen years of age, with left pulmonary tuberculosis. Pneumothoraxtherapy was being carried on with good results. At one session, when the operator was trying to increase the air content of the cavity, the manometer showed by its wide oscillations that the needle was in the right place. Air to the amount of 250 c.c. was injected. The patient became agitated, made a quick movement with her left arm, and suddenly fell unconscious. The needle was taken out immediately. The pulse could not be felt. Pale, with dilated pupils, the patient was breathing quite superficially. A circumscribed marble-like area on her left forearm was noted. Clonic contractions of all the muscles were followed by tonic cramps in the right upper arm. When she groaned, a palsy of the right facial nerve could be seen. For several hours she slept. Twitchings recurred several times, especially on the right side. She had an involuntary bowel movement. Death occurred after 3 days. Autopsy was refused.

Carpi,[36] when beginning the Forlanini technic on a patient who had been sick for 3 years, felt sure that the needle was in the pleural cavity. He started with 10 c.c.

of nitrogen. At this moment the patient complained of pains in the region of the puncture. She had a sensation of pressure, became unconscious, and had clonic convulsions on the right side, which later implicated the left side also. Trismus and opisthotonus were caused by these contractions. The respirations became frequent and superficial, with a pulse of 140. For a short time the patient was cyanotic, and sweated profusely. The pupils reacted to light. This attack lasted only a few minutes. After a short interval a second similar one followed. She made an uneventful recovery.

Before passing to the study of the etiology of these complications we shall consider the other procedures in which these serious accidents may occur.

Decortication (Delorme, Fowler) is advisable in cases of old empyema with a persistent sinus, to relieve the patient from the annoyance of a constant discharge of pus. Delorme's [37] procedure tries to avoid the great disfigurement of the Schede thoracoplasty by including the dense fibrous thickened visceral layer of the pleura of the lung, so that the lung can expand to its primary volume. This thick membrane holds the lung down in its contracted state. Fowler,[38] of Brooklyn, used the same technic at the same time without knowing of Delorme's procedure. A modification of this operation is Ransohoff's [39] discission of the pulmonary pleura for cases in which it is impossible to liberate the lung from its encircling coat. Parallel incisions are made a quarter of an inch apart, crossed by a second series perpendicular to the first. By this procedure expansion of the lung is probably rendered more gradual.

In these decortications many blood vessels, especially veins, in the superficial part of the lung are mechanically injured, the injuries being analogous to those that may be caused when irrigating this wall with a strong flow, or when introducing a tube into this cavity, which ploughs a groove on the surface of the lung (Brandes' observation). Confronted in all these cases with similar pathological changes of the pleura and neighboring lung tissue, we encounter a similar danger of air emboli (Weill).[40] In pneumothoraxtherapy we have an analogous process when in a partial pneumothorax one tries to break up some adhesions. These adhesions may become loose, and leave a defect in the superficial layer of the lung. The lumen of an opened vein may be kept open by its position in fibrous, dense tissue, so that the air comes into direct contact with the venous circulation. To diminish this danger Jacobaeus,[41] in 1913, devised an endoscope for the thorax, through which he burns off the adhesive strands along the costal pleura (thoracoscopy).

Careful precautions have to be taken in mobilizing the costal pleura, especially at the apex of the lung, when an attempt is made to insert a fat or a paraffin plug (Tuffier,[42] Baer [43]). The veins of these thickened pleuræ communicate with the veins in the adjacent lobe of the lung. The same danger is encountered in mobilizing the costal pleura for collapsing an empyema cavity, previously sterilized with Dakin irrigation.

In all the previously described operations the procedures were done near the chest wall. In pneumotomy and pneumectomy the operator comes nearer to the vessels at the hilus, with the larger veins under negative pressure, at least during inspiration. In these cases the possibility of complications from air embolism is always imminent, more so when sharp dissection is employed than when one comes up behind the necrotic wall with the Paquelin cautery or with a blunt instrument, such as the finger.

Passing through lung tissue with the cautery in attempting to reach a bronchiectatic abscess in a patient thirty-one years old, Quincke [44] was stopped by profuse bleeding. By means of gauze tampons the bleeding was controlled. The patient complained of a prickling sensation in both arms, and dizziness. He looked pale and collapsed with irregular, feeble pulse. The respirations became less frequent, and stopped. Fifteen minutes after the onset the patient was dead. At autopsy an open vein was found next to a bronchus which had been burned off by the cautery. The neighboring lung tissue was carnified.

Wever [45] cites a similar case of a girl, nineteen years of age, with bronchiectasis. The intention was to open the cavities in several stages. During one of the procedures the patient coughed and at the same time profuse bleeding occurred in the wound, which was stopped by gauze packing. The patient vomited and had tonic cramps in both arms. She was unconscious, and turned her eyeballs upward, with widely dilated reacting pupils. Marble-like patches, with a distinct outline, on the body and the extremities indicated definite vascular disturbance. The speech was dysarthric. A left-sided palsy of the facial nerve was noticed. For 24 hours she remained about the same, after which she gradually recovered.

To clear up the etiology of these complications we must consider the conditions in the normal pleura so far as they concern its sensibility. From a series of experiments which I began in the surgical clinic in Zürich, Switzerland (Professor Clairmont), and which are being continued in the Surgical Hunterian Laboratory (Professor Halsted) of the Johns Hopkins University, I have come to the following conclusions:

From irritation of the normal pleura of different animals, mechanical, chemical, or by the electric current, we do not get a constant specific reaction by way of the central nervous system, as we should expect if the so-called pleural reflexes were the real source of the above-mentioned complications in the different operations upon the chest. In the costal pleura we have sensory nerve fibres (intercostals), mechanical or chemical, irritation of which causes general protective movements, similar

to those which we see in other parts of the body (self-protection).

In smaller animals (rats, guinea-pigs, rabbits) faradic stimulation of the parietal pleura causes clonic contractions of the upper extremity of the same side. In dogs I have obtained only local contraction of the thoracic musculature, with no movement in the adjoining extremity. Faradic stimulation of the pulmonary or mediastinal pleura produces no muscular contraction at all in any of these animals. Stimulation of the diaphragmatic pleura with the faradic current gives only contraction of the diaphragm. This fact seems to indicate that the diaphragm gets its sensory nerve supply from the phrenic nerve only and not from the neighboring intercostals also. In dogs, as was stated above, even by irritating an area of the diaphragm next to the thoracic wall one gets only a contraction of the diaphragmatic muscle. No contraction is seen in the neighboring intercostal musculature. With faradic stimulation of the parietal pleura adjacent to the diaphragm in smaller animals, contractions are observed, in addition to those in the chest muscles, in the upper and lower extremity of the same side. In dogs only local muscular contractions are seen.

The vagus (pneumogastric) fibres running with the bronchi and all the branches of the bronchial tree carry pain sensation centripetally, causing protective movements in the upper extremity on the same side in small animals. After chemical irritation (with iodine) of the pleural cavity, the substance spreads through the pulmonary pleura into the lung. Resection of the vagus nerve in the neck inhibits these contractions. Stimulation or paralysis of the sympathetic nerve has no influence on these protective movements.

In all the cases of empyema in which these complications have been observed we have to deal with a long-standing condition. The pleura is thickened and covered with a granulating surface. The sensory nerve fibres in the area of the empyema cavity on the side of the thoracic wall are strangulated by mechanical pressure exerted by the encircling fibrous tissue. They are not functioning, and any reflex movements along these fibres are made impossible. Moreover, the lung tissue adjoining such a constantly discharging chronic infected cavity is altered and has become fibrous, as a consequence of reaction against the infection. In the majority of the cases of empyema, perhaps in all (C. Beck),[46] the primary focus of infection is in the superficial layers of the lung; the pleural cavity becomes affected secondarily. The fibrous tissue formation around an infected area represents a natural reaction of the body to combat the invading microorganisms. Around every lung abscess we have transformed tissue, partly infiltrated, partly fibrous, with the resultant changes around the blood vessels, particularly the veins with their weaker walls. The tissues about a bronchiectasis show similar changes.

In an empyema cavity the only sensitive elements are the sympathetic nerves, running with the blood vessels into fibrinous deposits which outline the wall. In the lung we have the vagus fibres along the bronchioli.

These are the pathological conditions which are found in variable degree and extent in all cases in which we are threatened with an air embolus. In tuberculosis of the lung we find similar changes taking place. But in that disease, in cases suitable for pneumothoraxtherapy, we do not find such uniformity of arrangement of the indurated tissue. Places showing little change are close to fibrous areas. In the center of the pathologically indurated areas we may have a cavity, or at least a circumscribed necrosis (caseous pneumonia). In these lungs we find all the different stages of the fight of nature against the invader. In all cases of air embolism the pneumothorax needle always passes into an area showing a specific process of natural repair. The pleura in these cases may be still very sensitive, if only relatively small parts of the lung are involved by the tuberculous disease.

In the wall of an empyema cavity with its underlying, chronically inflamed lung tissue, in the neighborhood of every active infection in the lung, the blood vessels are involved in dense fibrous tissue formation. In an earlier stage, when the infection is still active, the tissue shows a certain amount of infiltration. The vessels are suspended between the fibrous strands. There is a constant pull on these vessel walls when these fibres contract, especially on the veins. When their walls are mechanically injured, the veins cannot contract to the full extent, being hampered by their attachments in this inelastic tissue. The musculature of the vein, being weaker than that of the artery, is insufficient; the opening in the wall of the vein persists; from the hollow of the needle, or from the neighboring cavity (pleural cavity, bronchus) air or gas enters; and we have an air embolism. The result following any injury of the vessel wall shows the inability of these veins to contract to the same extent as they would do in normal tissue.

The blood in the lung gets its impulse from the right ventricle through the pulmonary artery. The sucking effect of the left atrium and the larger veins of the lungs is not so efficacious. The combined force of these two factors, together with the act of respiration, makes the current continuous. The sucking influence from the larger veins has a minor effect, in proportion as the vein is situated in the superficial parts of the lung, away from the hilus. A lesion of such a vein by an instrument allows the air, remaining under atmospheric pressure, (cavity, bronchus), or gas from a pneumothorax, to enter through the opening. The friction exerted by the air upon the vessel wall causes by reflex action a contraction of the

muscles innervated by the sympathetic nerves. This contraction is made ineffective by the attachment of the wall of the vein to the encircling fibrous tissue. At the same time this friction of air and blood along the wall stops the blood proximal to the air. This friction and the internal resistance of the air stops the movement in the blood column proximal to the lesion. No further movement is possible, unless the sucking action from a larger branch of a pulmonary vein comes to their assistance. The air embolism does not become clinically evident. This is the reason why this complication is not reported very often. In the different operations upon the chest wall a lesion of the veins happens quite frequently, but it does not make itself evident.

The force has to come from a larger vein under negative pressure in the neighborhood of the wounded vein in order to bring the air and the blood by aspiration into the left atrium. In several experiments on dogs the pressure in the pulmonary vein next to the hilus was tested with a manometer through an intercostal opening in the thoracic wall. The pressure was found to be —0.3 to —0.4 cm. water; i.e., negative. From the left ventricle the air can be dispersed all over the body. The air embolism renders itself manifest especially by the trophic changes in the brain and in the eye-grounds (retina). In the larger vessels the air causes a contraction of the wall; hence the smaller vessel may be closed at its junction with the larger vessel.

The distance between the point of the mechanical lesion of the vein wall and the junction of this vessel with a larger vein under negative pressure, whence the blood in the lacerated blood vessel, together with the air that has entered, can be aspirated, is the essential point in inaugurating the onset of a clinically manifest air embolism.

In cases of unilateral tuberculosis of the lung treated by artificial pneumothorax the injured vein may become connected only with the air in the needle. Then we have the conditions described above. But when the accident happens when the gas is flowing out from the apparatus under pressure, the air embolism is much more dangerous. These are the cases ending in sudden death, in which at autopsy we find a great number of gas bubbles in all the smaller vessels of the brain.

The mechanism of air embolism in an empyema cavity, caused by a change of a tube, the use of a probe, dilatation with a laminaria stick, irrigation, or injection, is well illustrated by Brandes' case, in which bismuth paste was found filling up the vein from the point of injury to a larger branch, with emboli in the capillaries all over the body, especially in the brain and in the intestine.

Mechanical injury of the blood vessel is facilitated in all abscess cavities by partial necrosis of the wall, caused by the continuous effect of the presence of pus. The blood vessels resist this process for a longer time, and therefore become exposed. Under these conditions a strong current of fluid may open a vein. A proof of this statement is that in the history of these cases we find that the fluid was observed coming back mixed with blood.

The recorded cases of air emboli in thoracoplasty have the same physiological and pathological underlying causes as empyemata. The knife or the blunt dissecting finger is always the primary faulty agent. To diminish this danger the use of the cautery was introduced, particularly for operations in the deeper part of the lung (bronchiectasis, pneumotomy). A path to the abscess cavity is made through the lung tissue by burning which closes all vessels by a thick escharotic membrane. Near the hilus even the Paquelin cautery cannot close the pulmonary veins tight, as was shown by the cases referred to above. By using the finger as a gently advancing dissector (Lilienthal)[47] this danger may be somewhat diminished. Moreover, we avoid the danger of a secondary hemorrhage when the eschars become loose in these infected wounds.

Complications showing a similar clinical picture may occur when we are performing the operations on the chest cited above, in which another cause for the complications is present. Without a thorough knowledge of the clinical features of air embolism, the physician can never be sure of the real source of these accidents. After all, a number of cases on the border line will remain undetermined.

We are constantly having to deal with patients who have lost weight and strength during a long illness. Complications from various sources arise much more easily in these patients, as they have no resistance. The quick release of a large amount of fluid out of a cavity in the chest can produce a collapse, caused by a temporary anæmia of the brain (empyema, ecchinococcus). In conditions with chronic inflammation of the lung, such as empyema, some veins may be blocked by thrombi (v. Dusch).[48] If they are mobilized during a therapeutic procedure, these clots follow the same course as the air, and we have a very similar clinical picture. Vallin,[49] in 1875, was the first to announce the opinion that these epileptiform attacks may be caused by capillary emboli from thrombi in pulmonary veins. Thrombi in the pelvic plexus or in the lower extremities may be mobilized during an operation. The pulmonary embolus gives a picture similar to that produced by a heavy air embolus. Autopsy will clear up the etiology. Chronic myocardial lesions may cause a collapse during an operation. The air embolus can be ruled out only by thorough examination. In a similar way insufficiency of the adrenals may become evident by a collapse with death. In only a few cases are the unimportance of the clinical signs and the short duration striking. The past history of these patients reveals a neurotic constitution. No

local signs of cerebral affection are seen. These conditions have a neuro-hysterical basis and are easily recognized.

The features of the clinical picture of air embolism following the different procedures mentioned above are so varied that is is very difficult to include them in a definite classification. Unfortunately, many of the histories of the reported cases do not mention several clinical features which we would expect in air emboli, and which would be of great importance in the differential diagnosis of these complications. More thorough examination of these conditions is necessary in order to furnish wider experience in such cases.

Pallor of the patient is often the first sign of imminent danger. Circumscribed patches of cyanosis on the skin present a marble-like appearance, a further proof of disturbances in the circulation. The patient complains of a sudden pain in the chest on the affected side. He cries out, saying that he feels giddy or ill and that he has black spots before the eyes. In many instances he becomes totally blind. Irritative pains in the injured side of the chest and severe headache aggravate the condition. The patient swoons, very often with no preceding aura. Unconsciousness comes on suddenly. The pulse is altered, perhaps cannot be felt any longer. Dyspnœa passes into stertor; the breathing becomes gasping; respiration stops. Involuntary evacuations precede the sudden death. In other cases pulse and respiration become very frequent. If the patient is still conscious, he complains of oppression in the chest. Later on the pulse becomes feeble. Respiration is of the Cheyne-Stokes type. The pupils are generally widely dilated, and do not react. In a few reported instances they were different on the two sides, perhaps with strabismus of the convergent or divergent type. If death occurs shortly after the onset of the complication, an autopsy should be done as soon as possible after death, to eliminate any post-mortem changes in the brain, the organ of greatest importance for the diagnosis.

After having passed through the stage of these preliminary symptoms, the attack may come to an end, the patient recovering gradually from his comatose condition.

In the majority of all cases clonic or tonic convulsions give evidence of an excitation of the motor areas, beginning in the eye muscles or in the upper extremity, and very often becoming generalized all over the body. Spasm of the back muscles gives rise to opisthotonus. From the histories of the reported cases it is impossible to trace a definite relationship between the affected side of the chest and the location of the most violent convulsions. In the literature we find the greatest variation in this feature. These contractions are followed by a paralysis, which varies in location and duration. Usually it lasts only a short time, from some minutes to several hours or several days. The palsy is generally most marked in the limb that is most affected by the convulsions, and remains there longer than in the other regions, perhaps even for months. The eye-sight is altered in an analogous manner, its return to normal being governed by a similar law. The disturbances in the sensory-motor region are shown also by circumscribed areas of hyperæsthesia and anæsthesia, and by different forms of paræsthesia.

Examination of these cases of air embolism discloses the fact that the clinical findings are quite variable. From a study of the pathology and physiology of these lesions we must try to trace the effect of the temporary embolism in different organs, the presence of which was indicated by the clinical pictures just described.

The ophthalmoscopic examination during an attack and later on at periodic intervals is of the greatest importance. The findings in the reported cases are divergent. Raynaud found in his case a serous suffusion around the papilla and a venous hyperemia. Schnitzler [50] noticed in de Cérenville's case a venous stasis combined with capillary hemorrhages. In the observation by Clairmont, which was published by me, no abnormality could be found immediately after the accident or later. In a case of air embolism following pneumotomy for gangrene of the lung, Becker [51] saw the air passing through the arteries of the retina in the form of gas bubbles. Later on, when the air was passing through the capillaries, strands in the form of fine white silver glittering lines filled the fundus. Subsequently the veins became enlarged. In the middle of the veins a white strand was seen (Stargardt).[52] The air seemed to be carried in the center of the vessel. After a short time the fundus looked normal again. Even after weeks changes caused by temporary thrombosis of the smaller arteries and capillaries can be seen. In cases with negative findings of the eye grounds the source of embolism may lie in the occipital lobe.

The clonic and tonic convulsions with subsequent palsy are due to nutritive changes in the motor area of the cortex. Partial temporary thrombosis in the medulla oblongata is followed by sudden death due to blocking of the vital regulative centers of respiration. The microscopic examination of the brain in these cases will show the cause of death. Spielmeyer [53] found liquefaction of the cells of the cortex as a typical condition. He noticed also an incrustation around the nerve cells of the nerve plexus. The glia reaction was negative. In cases in which death had occurred after several days, Spielmeyer found marked proliferation of the glia cells in circumscribed areas.

Air blocking the smaller blood vessels in the intestine (stomach, duodenum) causes a typical ulcer formation in the mucous membrane. This was found by Keller [54] in several cases at autopsy. When the patient has not partaken of meat before the operation which was com-

plicated by air embolism, a careful examination of the faeces during the following days will reveal traces of blood. Of course when the past history and the examination are suggestive of ulcer, or of tuberculosis of the intestine, this finding is of no use for the diagnosis of embolism. Albumin in the urine, and epithelial casts,—if they were not present before the accident—are quite significant of temporary nutritive blocking of the renal system.

Besides these different clinical findings the evidence of injury of a blood vessel during the diagnostic or therapeutic procedure is of the greatest value. Blood on the stylet after puncture is very suggestive of a lesion. The patient may have at the same time an attack of coughing, and spit up mucus mixed with blood. Bleeding during irrigation of an empyema cavity or during the changing of a tube in such a cavity is a sign to be noted as one of imminent danger. In thoracoplasty and in pneumotomy sudden bleeding is also of great diagnostic value. In all accidents accompanied by the symptoms described above we must think first of an air embolus, unless we can rule it out by the lightness of the attack in a patient who has a nervous make-up (nervousness, neurasthenia, epilepsy) and is weak from a long illness.

The *prognosis* in any case of air embolism after an operation on the chest depends upon the amount of air entering the blood stream, and also upon the region in the brain which is most seriously involved. The extension of the condition, especially to vital centers, causes sudden death. The clinical signs during the first attack give a fairly practical indication of the extent of the lesion. If the patient survives the first attack, the outlook is not bad, and he will gradually within a short time recover from all the bad effects of the accident. The time necessary for convalescence is proportional to the seriousness of the clinical picture at the onset. In the great majority of cases all the symptoms are temporary; as time goes on, they disappear. The air passes through the capillary system, causing a temporary blocking of certain areas in the brain, with concomitant nutritive changes. The heart action, which regulates the blood current, is very important in forcing the air through the capillaries, in this way diminishing the duration of the thrombosis in essential parts of the brain.

These points afford a sound basis for our therapeutic measures to combat the effects of these complications. The procedure that has been the source of the accident. must be stopped at once, thus removing the causative factor. The needle used in the puncture or injection or in the pneumothorax treatment is taken out. The irrigation in a case of chronic empyema is stopped. The tube or the probe causing the injury is removed. In pneumotomies where profuse bleeding shows that the vessel lesion is in the deeper part of the lung, packing the whole cavity with gauze will prevent the harmful air embolus. For these cases more particularly the use of a positive-pressure apparatus, to diminish the negative pressure in the larger pulmonary veins, recommended by Tiegel,[56] has proved to be very satisfactory.

When confronted by an air embolus the physician concentrates his attention on strengthening the heart and increasing the blood current through the brain, in order to force the air from the capillaries as soon as possible and to drive it to the lung, whence it can be expelled from the circulation through the alveoli. Intravenous injection of heart stimulants helps to strengthen the action of the heart muscle. An intravenous injection of adrenalin is followed by a contraction of the vessels of the splanchnic area (intestines) and the skin. This is a suitable and helpful procedure to improve the blood supply of the brain. The head should be put low, to increase the effect of this procedure. Jessen[57] has reported good results from a venesection.

If the breathing stops, rhythmic traction of the tongue and faradisation of the phrenic nerve should be employed. Artificial respiration is contraindicated, because deep inspiration might enlarge the opening in the vein and give rise to a new embolus. Morphine should never be used because of its paralyzing effect on the respiratory center.

As a useful prophylactic procedure, when doing these operations on the chest, bend the head of the patient to one side so that it is not the highest point of the body. With the head in this position, in case of air embolism, the air bubbles do not have the tendency to reach the capillaries of the brain. This was proved by experiments which I made on middle-sized dogs in the Surgical Hunterian Laboratory of Professor W. S. Halsted. The dog was put on his right side, flat. Under ether anæsthesia an opening was made in the left chest wall, in the fifth intercostal space. An injection of 2 c.c. of air was made into the pulmonary vein at the hilus. On ophthalmoscopic examination no air could be seen. A second injection of 2 c.c. of air was made. No air was seen passing through the blood vessels of the retina, but a gurgling sound was heard on squeezing the heart (left atrium). As soon as the dog was put in a semi-erect position, air bubbles appeared in the eye-ground. The dog died without any convulsions. This experiment was repeated with the same findings.

Summary

1. Following various diagnostic and therapeutic procedures on the chest (puncture, irrigation of a cavity, changing tubes, introducing a probe or a rubber catheter, bismuth paste filling, decortication, thoracoscopy, fat or paraffin plombage, pneumotomy, pneumectomy), complications may ensue which have been proved experimentally and clinically to be caused by air emboli.

2. The sudden release of a great amount of fluid in emaciated people with a neurotic constitution (neurasthenia, epilepsy) may cause a similar clinical picture. Because of its slightness and short duration, with lack of localized cerebral symptoms and serious sequelæ, this condition is considered to be due to shock.

Chronic myocardial lesions or an insufficiency of the adrenals may cause sudden death during the performance of one of these operations on the chest wall.

A similar clinical picture is seen in embolism of the pulmonary artery. Death, accompanied by these signs, may occur also in a few cases of emboli in the brain following thrombosis of pulmonary veins. The autopsy will clear up the diagnosis.

3. It was demonstrated by experiments that we do not have a pleural reflex, even in the normal pleura, which would explain these complications. They are proved by the accidents in pneumothoraxtherapy to be due to air emboli.

4. The pathological condition of the lung and the pleural sheaths is the same in all these cases. The lung tissue shows, in a circumscribed area, a condition which is partly an infiltration, partly an induration of the tissue, where the blood vessels, especially the veins with their weaker walls, are fixed in a distended position. When mechanically injured, they cannot, with these rigid surroundings, collapse as usual; the hole stays open. The distance of this wounded vein from a branch of a larger pulmonary vein under negative pressure, which can aspirate the air with the stagnating blood, decides whether the air embolism will become evident. Absence of this condition is the reason for the infrequency of air emboli.

5. The clinical pictures of these air emboli show a wide variety. They should be made more exact by further thorough study of these complications by means of ophthalmoscopic, stool, and urine examinations.

6. The best therapy is the preventive one. When an air embolus occurs, stop the operation immediately. Put the head of the patient low. Reinforce the heart action with stimulants. Adrenalin injections, administered intravenously, will increase the amount of blood passing through the brain by diminishing the blood supply in the splanchnic areas (intestines, skin).

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THE EFFECT OF SALINE PURGATIVES ON THE ABSORPTION OF OTHER DRUGS *

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Introductory

The present investigation was begun as the result of a personal experience. While suffering from an attack of the grippe one of the writers took for the relief of a severe headache a full dose of aspirin which had generally proved efficient for the purpose on other occasions. In the present instance no relief was experienced. The patient then swallowed a tablet of phenacetin and salol, also without relief. This was followed by five grains of pyramidon and this also did not prove any more efficient in the relief of the headache and pains than the other antipyretics. On pondering over the cause of the ineffectiveness of the above medication it was recalled that, before having recourse to the antipyretics, the patient had taken a saline purgative. It therefor occurred to him that possibly the saline purgative might have played a rôle in preventing or retarding the absorption of the drugs which were taken subsequently to it. It is well known that the pharmacodynamics of saline purgatives consists chiefly in the poor absorbability on the part of the intestinal walls of certain ions such as those of magnesium sulphate, phosphate, etc., and the accumulation of fluid in the intestines through the osmotic action of the unabsorbed salt which, instead of being absorbed, actually draws more fluid into the intestinal lumen. This peculiar property of the saline purgatives considered in connection with the above described clinical experience led the authors to inquire into the effect, if any, that such saline purgatives might have upon the absorption and excretion of other drugs given by mouth simultaneously with or subsequently to the taking of the laxative.

Phenolsulphonphthalein

Administration by Stomach Tube.—One of the most convenient drugs for beginning such a study was thought to be the dye, phenolsulphonphthalein. This drug, as is well known, is rapidly and completely excreted by the kidneys irrespective of the method by which it may be administered. The rate of excretion can be easily determined quantitatively by the colorimetric method; hence its widespread use as a kidney function test.

Accordingly, this drug was administered to a number of dogs with a given quantity of water through the stomach tube. At the end of two and one half hours the dogs were catheterized and the amount of phenolsulphonphthalein excreted by the kidneys in the two and one half hours was determined colorimetrically. A few days later the same animals were given exactly the same amount of phenolsulphonphthalein in exactly the same amount of water as in the previous experiments, but on

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this occasion the water contained 5 per cent of sodium sulphate in solution. The fluid together with the dye and sodium sulphate was administered through a stomach tube as before, and the total output of phenolsulphonphthalein was again determined at the end of two and one half hours. It was found that the amount of dye in the urine this time was less than one-half the amount excreted in the previous or control experiments. Similar experiments with phenolsulphonphthalein with and without sodium sulphate were performed on rabbits, with similar results; that is, it was found that the sodium sulphate solution markedly retarded the absorption and consequent excretion of the dye.

The same procedure was repeated on other occasions on both dogs and rabbits, but, instead of sodium sulphate, solutions of magnesium sulphate were used. It was found that this saline cathartic acted very much like sodium sulphate, in so far as it markedly retarded the absorption and excretion of phenolsulphonphthalein.

Experiments on Intestinal Loops.—In order to analyze the above phenomena more in detail, the following experiment was performed. A cat was anesthetized with ether, a laparatomy was made and the small intestines were exposed. Two loops of the small intestine, each 25 cm. long, were tied off, leaving the vascular supply intact. Into one of the loops there was injected 10 c.c. of a solution of sodium sulphate (10 per cent) plus 1 c.c. of phenolsulphonphthalein. Into the other loop was injected 1 c.c. of phenolsulphonphthalein in 10 c.c. of plain water. The abdominal wound was closed and the animal put in a cage. At the end of one hour the cat was killed with ether, the abdomen was opened again and the two loops of the intestine were examined. It was evident at once that one of the loops was greatly distended, like a sausage, while the other was collapsed. The two loops were excised and the fluid contents of each were measured. In the control loop, into which 10 c.c. of water had been injected, there were found only 1 or 2 c.c. of intestinal contents, whereas in the other loop, the one with the saline solution, the volume of the fluid had increased to over 30 c.c. Each loop of the intestine was washed out with water, the washings were combined with the fluid contents already obtained, and the amount of dye present in the intestinal loops was determined. It was found that whereas in the control over 50 per cent of the phenolsulphonphthalein had been absorbed by the intestine at the end of one hour, in the second loop there was present over 90 per cent of the dye. It was thus evident that the sodium sulphate had retarded markedly the absorption of the phenolsulphonphthalein from the intestinal lumen. This difference in absorption between the two loops was further strikingly corroborated by immersing each loop separately in a weak alkali. On treatment with the alkali, the mucosa of the normal loop became intensely red in color, showing that the dye had penetrated inside the cells. On the other hand, the second loop showed very little pink discoloration, thus indicating that very little of the dye had been absorbed. On extracting each intestinal segment with alcohol, the phenolsulphonphthalein in the tissues themselves was extracted, and a much greater amount of dye was obtained from the control loop. Several such experiments were performed with similar results.

Intramuscular Injections.—It was then thought possible, though by no means probable, that perhaps the administration of saline purgatives by the stomach might exert some effect on the excretion of phenolsulphonphthalein even if the dye were given by injection. Accordingly, to settle this point experiments were made first on some rabbits. The usual kidney function test was performed on two rabbits by injecting each of them with 1 c.c. of phenolsulphonphthalein intramuscularly. At the same time each animal received 50 c.c. of water through the stomach tube. The urine was collected at the end of the first hour and at the end of the second hour and the amount of dye excreted was determined by the usual procedure. A few days later each of the same animals was again injected with 1 c.c. of phenolsulphonphthalein intramuscularly, and simultaneously with the injection there was introduced through the stomach tube about 50 c.c. of water containing 5 per cent of magnesium sulphate. The output of the dye was again determined at the end of the first and second hours, and it was found that the excretion of phenolsulphonphthalein was markedly delayed in the experiments in which the salines had been administered by stomach. Precisely similar results were obtained with sodium sulphate.

Following these studies on rabbits, similar experiments were performed on three dogs. Phenolsulphonphthalein was first injected intramuscularly and the kidney function of the dogs was determined by measuring the dye output at the end of the first and second hours. A few days later the same dogs were given the same amount of dye by injection, but before the injection each dog received by stomach tube a quantity of sodium sulphate. It was found in the latter series of experiments that there was a distinct diminution in the phenolsulphonphthalein output. Following these experiments some days later another normal kidney function test was performed on the same animals, and two days later the same animals were injected with the dye and magnesium sulphate was administered by stomach tube. In this case also the phenolsulphonphthalein output was diminished or retarded by the administration of the salines. From the above experiments it was evident that the administration of saline purgatives by stomach, tended to retard the excretion of phenolsulphonphthalein, not only when given by mouth but also after injection of the drug.

Observations on Man.—Inasmuch as the phenolsulphonphthalein test is a perfectly harmless one, and inasmuch

as saline purgatives can be taken with impunity by almost every one, a series of tests were made to discover whether the above experimental findings hold good for man. Accordingly, a number of observations were made on the authors themselves, their colleagues and friends. The results obtained indicated that the administration of saline purgatives, definitely and in most cases markedly, affected the kidney output of phenolsulphonphthalein. More detailed results of these experiments appear elsewhere.[1] In this place it is sufficient to state that the conclusions drawn from a study of phenolsulphonphthalein are of immediate clinical importance, as may be illustrated by the following case described to the authors by a genito-urinary surgeon.

Protocol.—A middle-aged man came to a physician for treatment of the bladder. In connection with a routine physical examination, a phenolsulphonphthalein test for kidney function was made and to the doctor's surprise and consternation it was found that the phthalein output for the first two hours was very low, about 16%, thus pointing to a derangement of kidney function. The patient in question was in the habit of drinking every morning a dose of a well known bitter water. During the course of treatment he became tired of taking the above bitter saline purgative and changed about to a daily dose of compound licorice powder. It happened that the physician soon after made a second kidney function test and to his surprise he found that the kidney output had improved and was 38%.

The above history is not an unusual one. In the present paper, however, the research undertaken deals not so much with the influence of saline purgatives on the absorption and excretion of drugs administered by injection as with experiments concerning the effect of salines on the absorption and excretion of various drugs introduced into the stomach and intestines. A large number of drugs were studied in this connection and the results obtained are summarized briefly in the following pages.

Absorption of Potassium Cyanide

In order to put the above experimental data as obtained with phenolsulphonphthalein to a crucial test experiments were made with solutions of the powerful and rapidly acting poison *potassium cyanide*. In these experiments cats and dogs were kept under anesthesia, laparotomy was performed, and a loop of the small intestine was tied off without interference with the mesenteric circulation. A blood pressure tracing and a tracing of the respiratory movements of the chest were recorded on a kymograph. After preparation of the animals, a given dose of potassium cyanide solution in a definite amount of water (10 c.c. of 5% solution of KCN) was injected into the intestinal loop and the blood pressure and respiration curves were studied from the beginning of the injection until stoppage of the respiration and the heart of the animal. The time of death was then noted. In another series of animals the same procedure was carried out with the exception that the potassium cyanide was administered in a solution of sodium sulphate (10 c.c. of a 5% solution KCN in 10% Na_2SO_3). Blood pressure and respiratory tracings were taken again and the time of death was noted. It was found that, when potassium cyanide was given together with the sodium sulphate, its absorption and the subsequent picture of cyanide poisoning were greatly retarded, thus indicating that sodium sulphate tended to delay the absorption of the potassium cyanide by the intestinal mucosa. The following tracing illustrates one of the experiments. In this experiment potassium cyanide was injected into a loop of intestine together with sodium sulphate. It will be noted that the heart did not cease beating until about half an hour (36 minutes) after the injection of the poison. In control experiments, the same dose of cyanide injected in plain water solution produced death in about 7 minutes (Fig. 1).

In another experiment, after the injection of a 4% solution of potassium cyanide in 20 c.c. of sodium sulphate 10%, the animal lived 70 minutes, whereas the control dog, receiving the same quantity of cyanide in aqueous solution, died in seven minutes.

Absorption of Chloretone.

Chloretone was selected as representative of the hypnotic group of drugs. This drug has been used extensively in this laboratory as an anesthetic for cats and dogs. The effect of saline purgatives on the absorption of chloretone is most strikingly illustrated by the following experiments.

Exp. A.—A cat weighing 3 kilos was anesthetized with ether, laparotomy was performed and a loop of the small intestine, 20 cm. long, was tied off. Into this was introduced 100 mgms. of chloretone, per kilo weight of cat, dissolved in 20 c.c. of water. The abdomen was closed and the cat put in a cage. The effects of the ether anesthesia soon passed away but the anesthetic properties of chloretone quickly began to manifest themselves, so that before the end of an hour from the beginning of the experiment the animal was completely anesthetized by it.

Exp. B.—A cat weighing 3 kilos was anesthetized with ether as above, a loop of the intestines, 25 cm. long, was tied off, and into this was introduced a chloretone solution, 100 mgms. per kilo weight of cat, dissolved in 20 c.c. of a 5% solution of sodium sulphate. The cat was put in a cage. Effects of the ether soon passed away, but the anesthetic action of the chloretone did not manifest itself, and at the end of an hour the cat was sitting up quite contentedly. It was killed afterwards with ether.

Absorption and Excretion of Some Opiates

Several opium derivatives were studied in this connection.

Apomorphin.—It is well known that apomorphin produces vomiting when introduced by mouth or injected into an animal, through being absorbed into the circulation and carried to the vomiting center in the medulla. A number of dogs were first given small amounts of apomorphin hydrochloride (30 mgms.) dissolved in 50 c.c. of water. The onset of vomiting after the administration of the drug was noted. This varied for individual dogs,

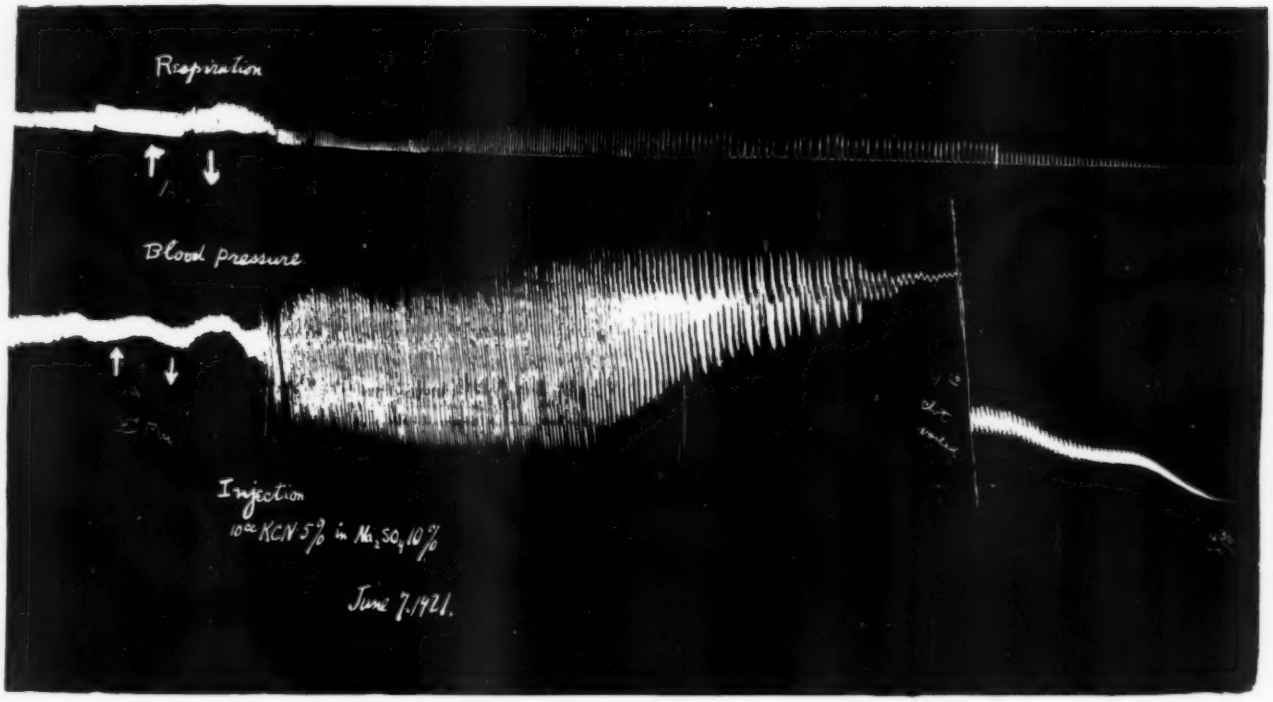

FIG. 1.—Experiment, June 7, 1921. Dog, 10 kilos. Ether anesthesia. Injected into intestinal loop 25 cm. long, 10 cc. of KCN 5% in a 10% solution of Na_2SO_4. Death occurred at 4.30 P. M. Beginning of injection was at 3.54 P. M.

but was pretty constant for any one animal. The same animals were given the same doses of apomorphin in the same volume of fluid on another occasion. In the second series of experiments, however, instead of water, a solution of sodium sulphate (5%) was used as a vehicle. It was found that in the latter series of experiments vomiting came on much later and some times not at all.

Morphine.—To study the effect of salines on the absorption of morphine the bimeconate salt was found to be very suitable. A cat was anesthetized with ether and two loops of the small intestine of about the same length were tied off. Into one of the loops were injected 10 c.c. of water in which was dissolved 50 mgms. of morphine bimeconate. Into the other loop the same amount of morphine bimeconate was injected but dissolved in 10 c.c. of a 5% solution of sodium sulphate. At the end of one hour the cat was killed, each loop of intestine was carefully cut out, and the intestinal contents of each were measured. The control loop at the end of one hour contained less than 1 c.c. of fluid. The loop containing the saline purgative at the end of one hour was found to contain about 35 c.c. of fluid. The contents of each loop plus the washings of the mucosa were then examined for the content of morphine bimeconate. After first coagulating the proteids and filtering, a colorimetric determination of meconic acid with ferric chloride was made. It was found by this method that the specimen from the loop containing sodium sulphate gave a much deeper color reaction for meconic acid than the control loop, thus indicating that much less of the bimeconate had been absorbed in the first case than in the control.

Pantopon.—The effects of pantopon on the respiration were studied. A rabbit was trained to lie quietly on a board without anesthesia and its rate and depth of respiration were registered by means of a stethograph. This rabbit was then given through a stomach tube 20 mgms. of pantopon in 20 c.c. of water. The results obtained are illustrated by the following protocol.

Rabbit—2000 grams.

11:30 A.M.—Respirations—58 per minute
11:45 A.M.— " —56 " "
11:50 A.M.— " —56 " "
11:55 A.M.— " —56 " "
12 M. — " —56 " "

Pantopon, 20 mgms. in 20 c.c. of water is introduced by stomach tube.

12:04 P.M.—Respirations—52 per minute
12:08 P.M.— " —50 " "
12:10 P.M.— " —48 " "
12:16 P.M.— " —46 " "
12:28 P.M.— " —44 " " and very shallow
12:35 P.M.— " —40 " " " " "
12:45 P.M.— " —40 " " " " "
12:55 P.M.— " —40 " " " " "

Exp. 2.—The same animal was used the following week and in this case the same amount of pantopon was administered by stomach tube, but mixed with 20 c.c. of a 5% solution of sodium sulphate.

Rabbit—2000 grams.

11:15—Respirations—52 per minute
11:30— " —50 " "
11:45— " —50 " "
11:48— " —introduced 20 mgms. of pantopon in 20 c.c. of sodium sulphate solution, 5%.

12 M.—Respirations—50 per minute
12:15— " —50 " "
12:30— " —50 " "
12:40— " —54 " "
12:45— " —54 " "
12:55— " —50 " "
1 — " —50 " "
1:30— " —50 " "
2 — " —50 " "
2:30— " —46 " " first effect of narcotic is noticeable.
3 — " —44 " "

The above protocols illustrate strikingly the difference in the narcotic action on the respiration due to the difference between the absorption of aqueous and saline solutions of pantopon.

Other Alkaloids

In addition to the opium derivatives a number of other alkaloids were tested. Among these were cocain, strychnin, atropin and quinidin.

Cocain.—The effect of saline laxatives on the absorption of cocain is illustrated by the following experiments.

Exp. Nov. 10, 1921.—Dog. 7.15 kilos. Ether anesthesia. Laparotomy was performed and a loop of the small intestine, 30 cm. long, was tied off. Into this loop were injected 10 c.c. of a 2% solution of cocain hydrochloride plus 20 c.c. of water. A blood pressure and respiration tracing was made and the first appearance of convulsions was noted. It was found that the cocain in this case very rapidly produced toxic symptoms, as indicated by failure in respiration, fall in blood pressure, and onset of tremors. Death occurred in 35 minutes after the injection of the alkaloid into the intestine.

Exp. Nov. 15, 1921.—Dog. 6 kilos. Ether anesthesia; laparotomy. A loop of small intestine, 50 cm. long, was tied off and into this were injected 20 c.c. of cocain-hydrochloride solution (2%) and 15 c.c. of a 5% solution of sodium sulphate. Blood pressure and respiration tracings were made and tremors and convulsions were looked for. There was no appreciable effect on the blood pressure or respiration or on the nervous system noted in the course of one hour from the time of injection. The dog was sacrificed later for another purpose.

From the above experiments it is evident that while in the control animal the loop was shorter in length and consequently the absorbing surface smaller and the amount of cocain injected was much less than in the saline experiment, nevertheless, toxic symptoms developed much sooner, thus very strikingly showing the inhibiting effect of sodium sulphate on the absorption of cocain hydrochloride.

Strychnin.—Experiments with strychnin were made on rabbits and dogs. The procedure was to tie off loops of intestine, inject a given dose of strychnin and note the first appearance of convulsions. It is hardly necessary to state that the experiments were performed under gener-

al anesthesia. It was found that when strychnin was administered in a solution of sodium sulphate the convulsions came on a little later than normally. Thus for instance, in one rabbit 4 mgms. of strychnin nitrate were injected into a loop of the small intestine, 15 cm. long, under paraldehyde anesthesia. The injection was followed by convulsions in 28 minutes. In another rabbit of the same weight the same dose of strychnin in a 5% solution of sodium sulphate was injected, and the convulsions did not set in until 35 minutes after injection. In dogs a similar difference in the time of onset of convulsions was noted. In all these experiments pains were taken to have the same degree of anesthesia in both the control and experimental animals, in order to eliminate differences in nervous response due to that source.

Atropin.—The effect of salines on the absorption of belladonna alkaloids is well illustrated by the following experiments.

Exp. May 11, 1922.—A cat was anesthetized with isopropyl alcohol by the method described by one of the authors elsewhere.[2] A loop of intestine, 20 cm. long, was tied off. Into this was injected a mixture of 4 c.c. of tincture of belladonna root plus 10 c.c. of water. The response of the heart to vagus stimulation with an induction coil was noted and the size of the pupils was also observed. It was found that the injection of belladonna produced a definite mydriasis in less than 5 minutes and paralyzed the vagus control of the heart within 10 minutes, after injection.

Exp. May 11, 1922.—A cat was anesthetized with isopropyl alcohol, as above. A loop of intestine, 25 cm. long, was tied off. Into this loop was injected the same amount of tincture of belladonna as above plus 10 c.c. of a 5% solution of sodium sulphate. The first appearance of mydriasis in this cat was noted after 15 minutes. The failure of vagus inhibition of the heart did not occur until after 20 minutes.

Quinidin.—Inasmuch as quinidin is employed extensively at present in the treatment of certain cardiac conditions, some experiments were made with this alkaloid. Equivalent amounts of quinidin sulphate were injected into loops of intestine, dissolved in water in some cases and in sodium sulphate solution in others. It was found by chemical tests that the absorption of this alkaloid was delayed by sodium sulphate. Very accurate quantitative determinations in this case, however, could not be made owing to the fact, emphasized by Lipkin[3] and others, that quinin and quinidin are rapidly decomposed in the intestinal canal. Ample evidence was nevertheless obtained to show a difference in absorption between the aqueous and saline solutions of the drug.

Heart Drugs

Digitalis.—Some 15 experiments were made with digitalis on cats. A sample of digitalis tincture was first assayed by the cat method and its minimal lethal dose was found to be 0.86 c.c. per kilo. This tincture was used in some experiments as such, while in others it was evaporated to drive off the alcohol and diluted with saline to the original volume. Experiments were made first by administering a large dose of digitalis through the stomach tube and determining the time of death with and without the addition of sodium sulphate. This method, however, was not found to be the most suitable on account of vomiting and other disturbances, and so resort was made to loop experments. In these experiments long loops of the intestine were tied off and a dose of digitalis sufficient to kill the animal was injected. Observations were then made on the rapidity of exitus with and without saline purgatives. The experiments were made under ether or isopropanol anesthesia.[2] The following protocols will illustrate the findings.

Exp. A.—Cat, 2.2 kilos. Ether was given and then isopropyl alcohol. After laparotomy a loop of intestine, 55 cm. long, was tied off without interfering with the circulation. Into this 10 c.c. of the evaporated tincture of digitalis were injected together with 20 c.c. of water. The injection was made at 2:35 P. M. The cat was dead at 4:30 P. M. The volume of the contents of the loop after death was found to be 20 c.c.

Exp. B.—Cat weighing 1.8 kilos. Anesthetized as above. After laparotomy, a loop of intestine, 60 cm. long, was tied off. Into this was injected 10 c.c. of evaporated tincture of digitalis plus 10 c.c. of water plus 10 c.c. of a solution of sodium sulphate (3%). The time of injection was 2:50 P. M. The cat lived until 8:45 P. M. The contents of the loop after death was found to be 50 c.c.

Exp. C.—Cat, 2.0 kilos. Anesthetized as above. Loop of intestine, about 50 c.c. long, was tied off. Into this was injected 10 c.c. of evaporated tincture mixed with 15 c.c. of castor oil. Injection was made at 10:25 A. M. The cat died at 11:55 A.M.

The above experiments as well as others clearly brought out the fact that when digitalis was administered together with saline laxatives its absorption and consequent toxic symptoms took place much more slowly than when the drug was administered with water.

Convallaria.—Several experiments were made on cats and dogs with fluid extract of convallaria. This drug was found to be much more toxic than digitalis, but the relative absorption with and without sodium sulphate was the same as in the case of digitalis.

Antipyretics

Of this group of drugs quite a number were studied and numerous experiments were made both on animals and men because one of them had been the starting point of the whole research. The following antipyretics were examined: sodium salicylate, salol, aspirin, antipyrin, acetphenetidin and lactophenin.

Sodium Salicylate.—The test for this drug being very simple, experiments with it were made both on rabbits and man. The drug was administered to rabbits in some cases by stomach tube, in other cases by intraperitoneal injections, and the time of the first appearance of salicyl in the urine was noted. In man sodium salicylate was administered by mouth and the time of the first appearance in the urine was determined in the same way. The test for salicyl was made by the addition of ferric chloride and the characteristic violet color was obtained. In doubtful cases the urine was acidified and shaken with ether and the test with ferric chloride was

repeated. It was found, both in the case of rabbits and in the clinical cases, that the excretion of salicylate in urine was markedly delayed by the previous or even simultaneous administration of various saline purgatives, such as magnesium sulphate, sodium sulphate and sodium and potassium tartrate. It was not delayed however, by the administration of other laxatives of the non-saline variety, such as castor oil and cascara sagrada. The following experiments will illustrate some of the findings.

Exp. A.—Rabbit weighing 1800 grams was catheterized and the urine tested with ferric chloride with a negative result. At 11 A. M., 5 c.c. of a 2% solution of sodium salicylate plus 20 c.c. of water was introduced into the stomach through a sound. The urine gave a positive salicyl test at 11:45 A. M.

Exp. B.—Rabbit weighing 1800 grams, with negative urine test, was given at 11 A. M. 5 c.c. of sodium salicylate (2%) plus 20 c.c. of a 1.5% solution of sodium sulphate. The first positive test for salicyl in the urine did not appear until 2:40 P. M.

Exp. C.—Rabbit weighing 2000 grams. At 10:15 A. M. introduced into stomach 20 c.c. of a 3% solution of sodium sulphate. 10:45 A.M. introduced into stomach 2 c.c. of sodium salicylate (2%). 11:50 A. M. salicyl test—urine negative. 12:45 P. M. salicyl test—urine negative. 2:30 P. M. salicyl test—urine negative. 3:45 P. M.—urine negative. No positive test was obtained that afternoon.

Exp. D.—Rabbit weighing 1500 grams, injected with 2 c.c. of a 2% solution of sodium salicylate intraperitoneally, at 3:05 P. M. Positive test for salicyl in the urine was obtained at 4:15 P. M.

Exp. E.—Rabbit weighing 1800 grams injected with 2 c.c. of sodium salicylate (2%) intraperitoneally at 3:15 P. M. Urine gave positive test for salicyl at 4:20 P. M.

Exp. F.—Rabbit weighing 2000 grams given 5 c.c. of cascara sagrada tincture in water by stomach tube, and this was followed by an intraperitoneal injection of 2 c.c. of a 2% solution of sodium salicylate, at 2:45 P. M. Urine gave a positive test for salicyl at 4:10 P. M.

Exp. G.—Rabbit weighing 1800 grams was given 10 c.c. of castor oil by stomach tube. 15 minutes later injected with 2 c.c. of a 2% solution of sodium salicylate intraperitoneally. Urine gave a positive test in one and a half hours.

Exp. H.—Rabbit weighing 1500 grams. At 1 P.M. given 15 c.c. of a 5% solution of sodium sulphate by stomach tube and simultaneously given an injection of 2 c.c. of sodium salicylate (2%) intraperitoneally. First indication of salicyl in the urine did not appear until 4 P. M.

Salol.—Experiments with phenyl salicylate, or salol, were made on man. As is well known, when this drug is administered by mouth, a positive test for salicyl is normally given in about an hour, to an hour and a half. It was found that the absorption and consequent excretion of salol was delayed by the administration of saline laxatives. Thus one of the authors was found to excrete the drug normally in a little over an hour. The same subject when taking salol after a previous dose of magnesium sulphate (½ ounce) did not give a positive urine test for nearly three hours.

Aspirin.—Experiments with aspirin or acetylsalicylic acid were made on animals and on man. It was found that the absorption of the drug was markedly delayed by the previous and even simultaneous administration of saline purgatives. In order to make sure of the first appearance of the salicyl after this drug, the tests for it were made with special care. In all cases whether dealing with urine or with other fluids the specimens were first hydrolyzed by the addition of a little sodium hydroxide and boiling, in order to make sure of breaking up all the aspirin into salicylic acid. Solutions were then carefully titrated and made very slightly acid and then definite quantities of ferric chloride were added.

The effects of salines on the absorption of aspirin are most strikingly illustrated by loop experiments. Cats were used in these experiments. Under anesthesia the abdomen was opened and two loops of the small intestine of approximately the same length were tied off. Into one of these 0.3 gram of aspirin suspended in water was introduced through a funnel and the loop was tied off. Into the other loop the same quantity of aspirin was introduced with the same amount of fluid but for this second loop instead of water a solution of sodium sulphate (2.5%) was used. The abdomen was closed and the cat was killed an hour later. The contents of each loop were carefully collected and measured. It was found in every case in which the aspirin was introduced in aqueous solution, that most of the fluid at the end of one hour had been absorbed. In the loops into which aspirin was introduced with sodium sulphate, the volume of fluid at the end of one hour instead of being decreased was actually increased to two or three times the original volume. The contents of each loop plus the washings of each loop were examined chemically for the amount of aspirin remaining in each and the quantity of the drug in each loop was compared colorimetrically. It was found that at the end of one hour about three times as much aspirin was absorbed from the loop with water than from the loop into which the aspirin was introduced with sodium sulphate. In other experiments, similar differences in absorption were found even after two hours.

Experiments with aspirin on man yielded very similar results. These experiments were made on a large number of students and also on the authors themselves. Aspirin was administered alone with some water, and some days later the same subjects took the same amounts of the drug with saline purgatives, such as magnesium sulphate, sodium sulphate, a Seidlitz Powder, or sodium phosphate. It was found that in most cases normally the first appearance of the salicyl in the urine occurred within one hour after administration of the drug. When, however, the aspirin was taken after a saline purgative, no positive test could be obtained from the urine within anywhere from three to six hours or longer. In fact, when the experiment was performed in the afternoon, no positive test could be obtained on that day. No such effect was noted after purgatives of the non-saline type.

Antipyrin.—A few experiments were made with antipyrin on man and on other animals. The drug was

detected by means of the ferric chloride reaction, which gives a red color, and the isonitroso test made by the addition of sodium nitrite, acidifying with sulphuric acid and shaking out with chloroform. Experiments on intestinal loops were performed with and without sodium sulphate and clearly indicated that the absorption of the drug was markedly delayed by the administration of sodium sulphate. The same phenomenon was noted after the administration of antipyrin by mouth to man.

Lactophenin.—The following experiment with lactophenin will serve to illustrate the effect of saline laxatives on the absorption of antipyretics belonging to the phenetidin group. Two loops of intestine were made in a cat and into each of these 50 mgms. of lactophenin was introduced, into one together with water, into the other together with a solution of sodium sulphate. After one hour the contents of each loop were tested for indophenol, by boiling with concentrated hydrochloric acid and treating with chromic acid. It was found that the sodium sulphate markedly delayed the absorption of the drug.

Potassium Iodide and Hexamethylenamine

These two drugs, it is well known, are among those which are most rapidly excreted by the animal organism. Not only are they very rapidly absorbed but they also very soon appear in most of the secretions of the body. In the urine hexamethylenamine can be detected within 20 minutes, while iodides appear in the urine in less than 10 minutes after ingestion. It was therefore with special interest that experiments were made with both of these drugs on man.

Hexamethylenamine (urotropin) was administered to a large number of normal subjects in doses of 0.5 gram by mouth and the time of the first appearance was ascertained. The same subjects on another day were given the same drug together with or following a dose of saline laxative and the time of the first appearance in the urine was compared with the normal. The test used was the so-called Hehner's test which detects both hexamethylenamine and free formaldehyde. It is performed by taking 0.5 c.c. of the urine and mixing it with an equal quantity of fresh milk and then stratifying it with 1 c.c. of 50% sulphuric acid containing a trace of ferric chloride. A violet ring very soon appears. It was found that, whereas normally after the ingestion of 0.5 gram of urotropin its excretion could be detected in the urine in about 15 minutes, the same subjects when taking the drug with a saline purgative showed a delay in the excretion. This delay was in some cases not very remarkable but in other subjects it was very striking, as may be illustrated by the following protocols.

Exp. D. M.—Given 0.5 gram urotropin together with a Seidlitz Powder. The first appearance of a positive test in the urine was 2½ hours after the administration of the drug. The normal time of appearance of the drug in the same subject was 20 minutes.

Exp. N. W.—Normal excretion of urotropin was 15 to 20 minutes. The subject was given half an ounce of magnesium sulphate and this was followed by 0.5 gram of urotropin. A faintly positive test was obtained 2 hours after administration.

Exp. C. K.—Normal excretion of urotropin about 20 minutes. Excretion after half an ounce of magnesium sulphate was 1½ hours later.

The experiences with *potassium iodide* were not so striking as those with urotropin. Twenty minims of the saturated solution were given to various subjects with and without saline purgatives. The normal excretion of iodide could be detected within 15 minutes. After the previous administration of magnesium sulphate a slight delay was observed. Thus, in one subject the first positive indication of iodide in the urine was one hour after ingestion. In another it was 45 minutes. In still others the drug could be detected in half an hour after taking by mouth. The test employed was by the addition of 0.5 c.c. of a 2% solution of sodium nitrite, acidifying with 0.5 c.c. of dilute sulphuric acid and then shaking out with chloroform. A positive test was indicated by a pink or violet coloration of the chloroform.

Antiseptics

Phenol.—Several years ago one of the authors in studying lavage in acute carbolic acid poisoning showed that the most suitable solution for lavage in acute carbolic acid poisoning was a saturated solution of sodium sulphate.[4] In the light of the present investigation the results obtained in this toxicological study of carbolic acid poisoning were not surprising. The sodium sulphate undoubtedly served two purposes: it not only served as a solvent for the washing out of the carbolic acid, but it also acted as a purgative and, above all, as an agent which tended to *prevent* the further *absorption* of the poison. This experiment with sodium sulphate solution in the treatment of carbolic acid poisoning prompted the authors in the present investigation to make some observations on the effect of saline purgatives on the absorption of mercuric chloride.

Bichloride of Mercury.—Two sets of experiments were made. In one series rabbits were used. To some of these an aqueous solution of mercuric chloride was administered by stomach tube. To others the same quantity of bichloride, proportionate to weight, was administered together with or following a previous administration of sodium sulphate. It was found, when a concentrated solution of saline was employed, that the animals succumbed more quickly in the first series of experiments than in the second. In other words, the sodium sulphate seemed to retard the absorption of the mercury and promote its elimination by purgation. The following two protocols may serve as illustrations.

Exp. Dec. 21, 1921.—Rabbit A, weighing about 2000 grams, was given by stomach tube 125 mgms. of mercuric chloride in 20 c.c. of water. The animal died in 12 hours.

Exp. Dec. 21, 1921.—Rabbit B, weighing about 200 grams, was given by stomach tube 125 mgms. of mercuric chloride in 20 c.c. of 7.5% sodium sulphate solution. The animal was alive on the following day, Dec. 22nd, when a similar dose of bichloride in sodium sulphate was administered. The rabbit died a day later.

In some of the experiments on rabbits the bladder was catheterized and an attempt was made to detect the presence of mercury in the urine. The method employed was similar to those described by Vogel and Lee [5] and later by Elliott.[6] A spiral of copper wire was placed in the urine and concentrated hydrochloric acid, 10 c.c. in 200 c.c. of urine, was added. The flask was thoroughly shaken and allowed to stand over night. The copper wire spiral was then heated in a small hard glass tube and any mercury that might be adherent to it was volatilized and allowed to deposit on gold foil. By this method the experiments seemed to indicate that more mercury was absorbed and consequently excreted in the urine of the control animals than in the case of those which had had a previous dose of sodium sulphate. Inasmuch as these experiments, however, were not very satisfactory, a quantitative study of the absorption and excretion of bichloride was made on cats by means of intestinal loops. Three such experiments were performed and in each case the figures obtained clearly indicated that the sodium sulphate distinctly retarded the absorption of the bichloride. The following protocols illustrate well these findings.

Exp. Dec. 26, 1921.—A.—A cat weighing about 3 kilos was anesthetized with ether. The small intestine was tied off just below the pylorus and again above the iliocoecal valve. Into this intestine was injected 50 c.c. of water containing 450 mgms. of mercuric chloride. The abdomen was closed and the animal was kept narcotized until its death which occurred in about *three* hours. The intestine was then cut out, its contents collected and the surface of the intestine thoroughly washed. The washings were mixed with the intestinal contents. The total volume of fluid was examined quantitatively for mercury.

Exp. Dec. 26, 1921.—B.—Another cat weighing about 3 kilos was treated in the same way as above. The whole small intestine was tied off above and below and 450 mgms. of bichloride were injected in 50 c.c. of 5% solution of sodium sulphate. This experiment was begun about 11 A. M. and the animal was still living narcotized quite late in the afternoon. The exact time of death was not noted, but the cat was found dead the following morning. The whole small intestine in this case was also cut out and the contents and washings preserved and worked up for mercury.

The macroscopical appearance of the intestines in Experiments A and B were quite different. The mucosa in cat A showed violent irritation. It was extremely congested and hemorrhagic and contained a bloody mucus. In cat B the intestinal mucosa appeared more normal. It was much paler than in the previous experiment and did not show so much irritation or hemorrhagic exudate.

Chemical tests for mercury were made by first treating the intestinal contents of each cat with concentrated hydrochloric acid and a little potassium chlorate. The solutions were boiled for several hours until all traces of chlorine had been driven off. They were then diluted in each case to the same volume. The solutions were then divided into two parts and examined for mercury by two independent workers. The mercury was precipitated with hydrogen sulphide and filtered through Gootch filters. The sulphide was then weighed. The quantity of mercuric sulphide obtained in Experiment A was 105.6 mgms. an amount equivalent to 123.24 mgms. of mercuric chloride. The mercuric sulphide obtained from the intestinal contents of cat B was 141.2 mgms., an amount equivalent to 164.78 mgms. of mercuric chloride. The difference between the above figures indicates that less mercury was absorbed from the intestine containing the sodium sulphate than from the one in which the bichloride had been introduced in aqueous solution. Two other sets of experiments on cats yielded similar quantitative differences.

DISCUSSION

The experiments described above are quite sufficient to establish beyond doubt that saline purgatives can and do affect markedly the absorption and consequent excretion of other drugs. Bearing in mind the pharmacodynamics of saline purgatives such a result is not altogether surprising when both the saline and other drugs are administered by mouth or introduced into the intestinal lumen. More remarkable, however, are the findings in the case of *injections* such as were made with phenolsulphonphthalein in man and in other animals and with sodium salicylate in rabbits. It is evident that the absorption and excretion of drugs are influenced to some extent by saline laxatives even when such drugs are given by injection after the purgatives have been previously administered by stomach tube. The explanation of this phenomenon is not altogether clear. Undoubtedly, however, it must have something to do with the concentration of the blood and the distribution of fluids in the body. It has been known for some time that saline purgatives will concentrate the blood, as is indicated by the blood count, and this has been recently emphasized by the work of Underhill.[7] This probably plays a rôle in the phenomena studied in this paper. The findings obtained are of an immediate practical interest. It is evident that it is not immaterial whether drugs are administered with or without certain cathartics. The salines will markedly retard the absorption of many drugs, such as antipyretics, digitalis, etc., and the therapeutic results expected in clinical cases may consequently not be attained. The authors have studied the relation of other laxatives such as calomel, cascara sagrada, castor oil, etc., in this connection but have not found any important influence exerted by these drugs on the absorption and excretion of other medicaments. The exact *duration* of the inhibitory effect of saline purgatives on the intestinal mucosa has not been made a subject of exhaustive study by the authors. It will, of course, vary with the drugs and the

purgatives used and also with the individual subject. This inhibitory or retarding influence on the absorption of medicaments should, however, be born in mind by the careful clinician who may wish to obtain a prompt response on the part of the patient to the effects of any given medication.

Another important bearing which the above findings serve to reveal is the usefulness of saline purgatives and lavage with saline purgatives in cases of poisoning. Such a procedure is certainly an innocuous one and in the light of the present investigation would tend to minimize the absorption and promote the expulsion of any toxic substances remaining in the intestines.

SUMMARY

1. The absorption of a large number of drugs from the gastro-intestinal tract was studied by chemical and physiological methods in animals and in man.

2. It was found that all the drugs examined were markedly delayed in their absorption from the stomach and intestines when they were administered subsequently to or even simultaneously with saline laxatives.

3. The absorption and subsequent secretion of phenolsulphonphthalein and sodium salicylate were markedly affected by saline purgatives, even when the former drugs were administered by intramuscular or intraperitoneal injection.

4. Laxatives other than those of the "saline" type exerted no important effect on the absorption of the drugs from the stomach and intestines.

5. The above findings have an important practical bearing on the therapeutic administration of medicaments.

6. The above experiments, especially those with phenol and mercuric chloride, furthermore, speak in favor of a more extensive employment of saline laxatives in the treatment of toxicological cases.

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LOCALIZATION OF CUTANEOUS NERVES BY ELECTRICAL STIMULATION, APPLIED TO NERVE-BLOCK ANAESTHESIA

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In a report published in the Anatomical Record,[1] the author described a new method of teaching the distribution of cutaneous nerves to students in Gross Anatomy. This procedure, suggested by the work of Trotter and Davies[2] on cutaneous sensibility, consists of stimulation of the cutaneous nerves through the skin with a unipolar electrode. By this means, the point of emergence of the cutaneous nerve from the deep fascia and the subsequent course can be easily identified; the area of distribution of the nerve is clearly outlined by the tingling sensation.

With the rapidly increasing use of local anæsthesia in surgical procedures of all kinds, methods have become pretty well standardized. Any suggestions, therefore, can now be expected only to add some refinement to a technic which in expert hands is already nearing perfection. The intelligent use of local anæsthesia in its wide field of application requires a highly specialized knowledge of the distribution of all cutaneous nerves. Though any region may be affected by the use of paravertebral nerve-block, this method is not always justified by the scope of the surgical procedure. Simple regional anæsthesia has many advantages over the more generally used infiltration-method which need no exposition here, and has been widely used since the publication of Cushing's paper in 1900.[3] It is to the former type of anæsthesia that this method of accurate localization of nerve trunks can be applied.

The suggested method in no way absolves the operator from the necessity of being familiar with the general position of the nerve trunks. No amount of knowledge, however, can prepare one for the individual variations which are constantly met with in the position, point of emergence from the fascia, and above all the ultimate distribution of superficial cutaneous nerves. These variations may occur even on opposite sides of the same individual and undoubtedly are responsible for many of the unsatisfactory results obtained in block anæsthesia.

To meet these difficulties such a localization of cutaneous nerve trunks furnishes a method of almost absolute accuracy. A single dry cell, a small induction coil,* and an indifferent and a stimulating electrode constitute the entire apparatus needed. A faradic current too weak to cause muscular contraction will give the tingling sensation over the entire distribution of the nerve when the stigmatic electrode is applied immediately over the nerve trunk. When the anatomical position of the nerve trunk

* Harvard Instrument Company.

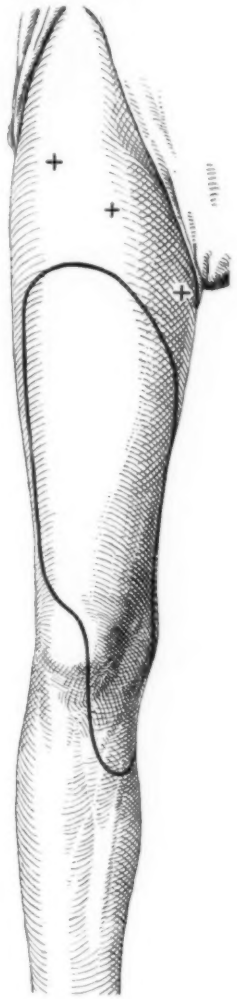

FIG. 1.—Localization of Cutaneous Nerves by Electrical Stimulation, Applied to Nerve Block Anæsthesia.

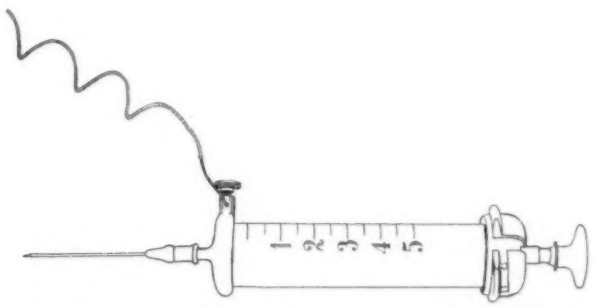

FIG. 2.—Localization of Cutaneous Nerves by Electrical Stimulation Applied to Nerve Block Anæsthesia.

is abnormal or when there is some uncertainty as to its exact location, careful search with the stigmatic electrode over the expected area invariably reveals the nerve. Sensory nerves over practically the entire body can be located in this way.

Having determined the size of the area to be anæsthetized and located the nerve trunks supplying the region, the injection of novocain, or any other appropriate drug, at the points determined will give the required anæsthesia over the entire area of the cutaneous nerve.

With this accurate localization the point may be marked on the skin † at any time previous to the operation, as in the ward by the interne, and the surgeon is required simply to inject the anæsthetic at the points indicated. Smaller amounts of the anæsthetic are sufficient when injection is thus made either directly into the nerve sheath or into its immediate vicinity. The illustration (Fig. 1) is made from a case in which 0.5 c.c. of novocain was injected at each of the points marked by a star. The resultant cutaneous anæsthesia involved the whole anterior surface of the thigh, as shown by the black outline, and lasted for a period somewhat over two hours.

Even greater accuracy may be obtained when injecting the anæsthetic by using the hypodermic needle as the stimulating electrode, a suggestion made by Dr. H. H. Young. This can readily be done by simply soldering a fine copper wire to the needle or by the use of a specially prepared hypodermic syringe as shown in Figure 2. To the outlet of the syringe there has been attached a small set screw which readily permits making the necessary connection with the induction coil, and in addition does away with the somewhat awkward needle and wire; the latter however has the advantage of being very easily made. It is not necessary to insulate the needle when used in this way. After insertion of the needle through the skin at the pre-determined points, a weak current is passed through the needle as stigmatic electrode and the nerve trunk located with remarkable accuracy. Deviation of the needle-point less than a millimetre to either side of the nerve trunk will cause a loss of the stimulating effect. When the nerve has thus been positively identified, the anæsthetic may be injected. Prompt dulling and then complete loss of sensation results. The procedure is in no way painful. Actual stimulation of the nerve trunk with this mild current causes no more intense sensation than stimulation through the skin. This method is also applicable to nerve trunks lying deep in the muscle tissue before they have emerged from the fascia.

Of course, no new principle is involved in the method suggested; it is simply a refinement of one branch of the general technic of producing local anæsthesia by the injection of a drug in the region of the nerve trunk. This method has not been used for actual clinical purposes but sufficient direct observations have been made to indicate that it can have definite practical use in a great variety of surgical procedures. This is particularly true as regards the extremities and the neck. A certain amount of intelligent cooperation on the patients' part is necessary but this can readily be obtained by first demonstrating the sensation to be expected by stimulating some obvious trunk such as the ulnar or radial.

† We have used an excellent indelible skin-ink for this purpose, described by N. S. Finzi, Brit. M. J. I, 52, Jan. 12, 1918.

CONCLUSIONS

Localization of sensory nerve trunks by unipolar stimulation through the skin furnishes a method whereby nerve-block anæsthesia can be produced with the greatest accuracy and certainty. Difficulties due to anatomical variations are done away with and the surgeon is enabled to deal with each case individually. The apparatus required is easily prepared and the procedure is in no way painful or unpleasant to the patient.

FIGURE LEGENDS

FIG. 1.—Crosses indicate position of nerve trunks and points of injections of anæsthetic. Black line outlines area of anæsthesia obtained.

FIG. 2.—Record syringe fitted with set screw for attachment of wire.

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THE EFFECT OF SODIUM GERMANATE UPON THE TOTAL HEMOGLOBIN OF THE ALBINO RAT

By Joseph E. Nowrey, Jr.

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In a previous publication it has been shown that germanium dioxide in alkaline solution is non-toxic and non-corrosive for the tissues of the albino rat when administered by subcutaneous injection.[1] It has also been pointed out that such a solution will cause a marked increase in the number of erythrocytes in the peripheral blood when administered in the same manner.[2] A further study has demonstrated that this rise in the red blood corpuscles is accompanied by an increase in the number of nucleated red cells in the bone-marrow of these animals, indicating that stimulation of the erythrocytogenic tissue has taken place as the result of the action of this compound.[3]

The physiological action of germanium compounds is, at present, almost wholly unknown. In spite of the evidences of increased bone-marrow activity obtained from the examination of histological preparations, it was thought possible to settle the question of a real or an apparent increase in the number of the erythrocytes in the blood. If there were a real increase in the number of erythrocytes, the total hemoglobin should be higher in treated animals than in normals, providing the hemoglobin parallels the red cell count.

The purpose of the present study was to determine what change, if any, takes place in the total amount of hemoglobin in the blood of the albino rat after the administration of germanium dioxide in alkaline solution.

Experimental

One gram of chemically pure germanium dioxide was sifted into 200 milliliters of distilled water. Sufficient normal sodium hydroxide was then added to dissolve the oxide, and make the solution distinctly alkaline. The excess of alkali was neutralized by the addition of enough normal hydrochloric acid to bring the solution back to a pH of 7.0-7.2. The solution was then sterilized by boiling, and after cooling the volume was made up to 250 milliliters by adding sterile distilled water. The addition of the alkali converted the dioxide into sodium germanate according to the equation:

$$GeO_2 + 2NaOH = Na_2GeO_3 + H_2O.$$

As will be shown in a future paper, it is in this form that germanium is most efficient as an erythropoietic agent. The addition of an excess of alkali is therefore imperative.

Two series of mature rats were selected, one series of seven animals being used as tests, and the other series of six reserved as controls. Red blood cell counts and hemoglobin estimations were made on the rats of both series, and immediately after these were completed, the test rats were injected with a dose of 17 milligrams of the sodium germanate solution per kilo of body weight. This is equivalent to a dose of 10 milligrams of the dioxide per kilo.

For a period of three weeks preceding, and during the course of the experiment, the rats received the same varied diet, in order to safeguard against any variations in the action of the germanate solution that could arise from dietary influences. The work of Hooper, Kolls, and Wright[4] shows that fasting and various diets will strongly influence the action of arsenic compounds; and it is quite possible that the same factors have an influence on the action of other substances.

One week after the initial counts and hemoglobin determinations were made, the red cell counts were repeated and the hemoglobin redetermined on the rats of both series. Immediately after this was done, total hemoglobin determinations were made on all the animals, employing the following technique which is a modification of the method described by Jaquet and Suter.[5]

The rat was placed under ether anæsthesia and tied to a small animal board by its four extremities. The board was fastened upright over a large beaker in such a manner that the blood and perfusing fluid would drip directly and without loss into the vessel. The ventral surface of the rat was then washed with a five per cent solution of sodium citrate in order to prevent the blood from clotting on the animal's fur. The abdominal and thoracic cavities were then opened by a large inverted T-shaped incision. These cavities were immediately flooded with the sodium citrate solution in order to lessen the tendency toward clot-formation.

While the heart was yet beating, the left ventricle was opened, and a cannula was inserted through the ventricle and into the aorta, and held firmly in place by a ligature. Precaution was taken not to allow the tip of the cannula to pass into the subclavian or carotid arteries, as this would cause an incomplete perfusion. A clamp held the cannula in position and kept its weight from dragging the aorta out of place. The hepatic vein was then cut at its site of emergence from the liver, and the perfusing fluid, physiological saline, was allowed to pass through the animal's vascular system. As soon as the fluid had begun to circulate, the rat was suspended by means of a cord tied around its upper incisors, and the ligatures were removed from its extremities, in order to facilitate the return flow of blood from the feet. The reservoir con-

taining the perfusing fluid was placed at a height of two meters above the animal's heart.

The perfusion was allowed to continue until the fluid leaving the animal was colorless. By this time the liver and kidneys were very pale in color and practically bloodless. An interval of from two and one-half to three and one-half hours was necessary to accomplish this, and from 1000 to 1400 milliliters of the perfusing fluid were required to complete each perfusion.

The blood volume of the rat was then estimated by means of Hatai's formulæ [6] which are based on the work of Chisolm.[7] These formulæ are as follows:

1. For rats under 150 grams body weight, (Both sexes)
   Blood volume, (in c.c.) = (Body weight in grams)$^{0.9}$ × 0.099.
2. For male rats 150 grams and over,
   Blood volume, (in c.c.) = (Body weight in grams)$^{0.9}$ × 0.09608.
3. For female rats 150 grams and over,
   Blood volume, (in c.c.) = (Body weight in grams)$^{0.9}$ × 0.10494.

On the basis of this estimation sufficient distilled water and hydrochloric acid were added to the perfusate to obtain a final dilution of one part of blood in 250 parts of tenth-normal hydrochloric acid. The action of the hydrochloric acid converted the hemoglobin into acid hematin. The estimation of the total hemoglobin was made directly from this dilution, using the permanent glass standard described by Newcomer.[8] The preliminary hemoglobin determinations were made by the same method.

In this experiment the red cell counts were determined from samples of blood drawn from the tip of the animal's tail. This method is, in the writer's opinion, the method of choice for the purposes of the present study, and preferable to the method of obtaining the sample of blood directly from the heart of the rat. The danger of puncturing the pleura is very great in such a small animal, and as Bürker, Ederle, and Kircher have shown,[9] the production of a unilateral artificial pneumothorax causes a true polycythæmia, and such an accident would nullify the results of his experiment.

Results

The results are summarized in the tables.

Following the injection of the germanate solution there was a marked rise in the number of erythrocytes in the peripheral blood of the test rats.

It will be seen from the tables that in the control animals, the hemoglobin readings, as determined by using a measured quantity of blood, and those obtained from the perfusate diluted on the basis of Hatai's formulæ, are consistent. This would indicate that for the normal rat, the blood volume may be estimated within a reasonable degree of accuracy by the use of these formulæ. In the test rats, however, on comparing the hemoglobin readings obtained by the two methods, considerable discrepancy was noticed, as the estimated concentration of hemoglobin obtained from the total hemoglobin determination was always higher than that obtained from a measured sample of blood. It was apparent, therefore, that Hatai's formulæ could not be used to estimate the blood volume of the rats treated with the germanate solution. The most plausible explanation of the discrepancies between the partial and the total hemoglobin determinations in these animals is the assumption that an increase in the blood volume has occurred.

This experiment, then, furnishes an additional evidence that the increase in erythrocytes following the injection of sodium germanate is due to a true erythropoiesis and is not a relative effect due to a simple concentration of the blood plasma, such as Bertelli, Falta, and Schweeger,[10] and Lamson [11] have shown to occur after the administration of epinephrin. The results of the present study show clearly that no concentration of the blood plasma has occurred, for if such were the case, the concentration of hemoglobin based on a normal blood volume would be lower in the total hemoglobin determinations. Since these, on the contrary, show a distinct tendency to run higher than the corresponding readings obtained from a measured amount of blood, there is furnished a strong indication that the blood volume is increased following the injection of sodium germanate solution.

Summary and Conclusion

Two series of albino rats were taken. One lot of seven animals was used as tests, and the other series was reserved as controls. Red cell counts and hemoglobin estimations were made on all, and the test rats were then injected with 17 milligrams of sodium germanate per kilo of body weight. One week later red cell counts and hemoglobin readings were done again on all. The rats of both series were then perfused and total hemoglobin estimations were made from the diluted perfusates.

A study of the results shows that in the controls there was no significant change in the red cell counts, in the hemoglobin concentration, or in the blood volume. In the test animals there was a marked increase in the number of erythrocytes per cubic millimeter of blood, a moderate increase in the concentration of the hemoglobin, and a variable increase in the blood volume. There was no evidence of a concentration of the blood plasma in any of the animals.

It is therefore concluded from this and the preceding papers that the increase in the red cells of the blood of the rat following the injection of sodium germanate is in all probability due to a stimulation of the bone-marrow and not an effect which follows a concentration of the plasma.

TABLE I.—CONTROLS.

	First Determination.			Second Determination.					
	Weight in grams	R. B. C. count, in millions	Hemoglobin, gms. per 100 c.c.	Weight in grams	R. B. C. count, in millions	Hemoglobin, gms. per 100 c.c.	Total Hemoglobin, gms. per 100 c.c.	Blood volume, c.c., calculated from Hatai's Formula	Blood volume, corrected
1.	167.	9.00	10.63	177.	9.25	9.94	10.09	9.62	9.72
2.	188.	8.10	12.01	195.	8.28	11.73	11.83	11.06	11.16
3.	179.	7.97	11.73	181.	8.00	11.73	12.10	10.34	10.66
4.	241.	8.43	11.87	245.	8.56	11.73	11.59	13.58	13.42
5.	137.	8.52	11.04	137.	8.73	11.45	11.65	8.29	8.43
6.	232.	8.50	10.35	240.	8.64	9.73	10.74	13.32	13.82
Mean.	190.6	8.42	11.27	195.8	8.54	11.05	11.33	11.03	11.20

TABLE II.—TESTS.

	First Determination.			Second Determination.					
	Weight in grams	R. B. C. count, in millions	Hemoglobin, gms. per 100 c.c.	Weight in grams	R. B. C. count, in millions	Hemoglobin, gms. per 100 c.c.	Total Hemoglobin, gms. per 100 c.c.	Blood volume, c.c., calculated from Hatai's Formula	Blood volume, corrected
1.	256.	8.30	10.35	260.	9.93	11.04	16.32	14.29	21.13
2.	240.	7.84	10.76	253.	9.12	11.73	12.70	15.17	16.42
3.	219.	7.64	10.90	228.	9.18	12.01	12.77	13.90	14.96
4.	192.	8.06	11.73	190.	9.24	12.42	13.81	10.80	12.01
5.	200.	9.28	12.14	215.	10.07	12.42	13.62	11.79	12.92
6.	113.	7.27	10.63	124.	9.62	11.32	12.67	7.58	8.48
7.	148.	7.74	10.21	161.	9.58	11.04	13.44	9.30	11.32
Mean.	195.4	8.02	10.96	204.4	9.52	11.71	13.62	11.83	13.89

The two determinations were made one week apart.

The sodium germanate was injected into the test animals immediately after the first determination.

I wish to thank Dr. A. C. Kolls for many helpful suggestions.

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GIANT CENTROSPHERES IN XANTHOMATOUS TUMORS

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When normal cells begin to degenerate in tissue-cultures a series of very characteristic but complicated changes takes place. The mitochondria break up into fine granules, form vesicles, or disappear entirely (Lewis and Lewis, 1915);[1] in some cells there is a great accumulation of granules and vacuoles which stain with neutral red (W. H. Lewis, 1919),[2] while in others the most striking feature is the formation of a giant centrosphere (W. H. Lewis, 1920).[3] It is with the evidence of degeneration afforded by the latter that we are concerned in this communication. The centriole in tissue-culture cells that have been fixed and stained seems always to be in the form of a granule, single or double, usually the latter. The peculiar differentiated region around the centriole is called the centrosphere and corresponds to the central body, the aster, or astrosphere of the dividing egg and cell (W. H. Lewis, 1920).[3] This structure is at one side or one end of the nucleus and generally in direct contact with it. Dr. Lewis found that the mitochondria and degeneration granules have a marked tendency to arrange themselves around the centrosphere and to move in radiating paths to and from this structure. The pigment in true pigmented cells, as well as pigment granules that have been taken in as foreign bodies, shows the same peculiar arrangement about the centriole and centrosphere. When the cell begins to degenerate under certain conditions, the centrosphere increases enormously in size, becoming as large as or even larger than the nucleus. In this giant centrosphere Dr. Lewis distinguishes a centriole, single or double, immediately surrounded by a clear medullary zone, and beyond this a larger cortical zone. The granules and vacuoles are arranged about this outer cortical zone.

In studying a group of xanthomatous tumors which contained many giant cells, much blood pigment from other cells, and numerous foam cells, the writer noted that the granules in the pigment-bearing cells were arranged about a clear area, often the size of the nucleus

or a little larger, which occupied the center of the cell and displaced the nucleus to one side (Fig. 1). By careful focusing it could be determined that this clear area was a spherical body, one portion of which was in direct contact with the nucleus (Fig. 2), and that around this sphere was an outer shell of granules, complete except where it came against the nucleus. Often the cells were so filled with granules as to obscure all other cellular structures (Fig. 1). In the sections from which the figures here shown were taken (Surg. Path. No. 3890), nearly all the pigmented cells contained these clear central areas. A few cells showed an accumulation of granules to one side of the nucleus without the formation of this area (Fig. 3).

In several types of cells in tissue-cultures the neutral red granules which accumulate in degenerating cells are at first scattered; later they begin to collect near the nucleus, probably about the centriole. Later still, as the mass of granules increases, a clear centrosphere forms in the center of it, the granules surrounding its periphery. In xanthomata there are indications of a similar process, of which Figure 3 probably represents an intermediate stage before the appearance of the clear central area. Earlier stages were seen, but most of the cells were in the later stages and contained centrospheres of various sizes. Owing to the fact that the cells are orientated at various angles in the plane of the section, some cells, especially those in which the nucleus and centrosphere are parallel to the plane, show these relationships much better than the others. Although no definite structures can be made out in these spherical bodies, such as have been described by Dr. Lewis in tissue-culture cells, it is evident that we are dealing with giant centrospheres in these xanthomatous tumors. The details of the structure in the giant centrosphere cannot always be seen, as was shown by Lewis and Webster (1921) [4] in their study of giant cells in cultures from human lymph-nodes.

Seventeen xanthomatous tumors were studied with special reference to the presence or absence of these giant centrospheres. The latter were present in nine, or a little over 50% of the cases. Of these, seven also contained foam cells, which have been regarded as evidence of degeneration of tissue (C. Smith, 1912).[5] One specimen (Surg. Path. No. 5151) contained foam cells but no giant centrospheres. The cells containing the pigment appeared very degenerate and it is possible that they had reached that late stage in the process in which the giant centrosphere is lost, as has been described by Dr. Lewis (1920) [3] in tissue-cultures. There were eight tumors in this series which had neither giant centrospheres nor foam cells. In the cells of these tumors the nuclei stained well, the growth seemed active and there was no evidence of degeneration.

It is well known that pigment occurs in several types of tumors and it was therefore thought advisable to examine some of these to ascertain if the giant centrosphere is present in all, or if it is a special characteristic of the xanthoma group. The study included 25 benign pigmented moles, 50 malignant pigmented tumors, 20 giant-cell tumors of bone containing blood pigment, and 10 bone sarcomata containing blood pigment.

In some of the cells of the moles it could be seen that the granules were grouped at one side or one end of the nucleus, about what was probably the centriole, but there was no evidence of a giant centrosphere.

In the pigmented tumors many of the tumor cells were undergoing degeneration, but although the pigment frequently appeared to be collected about the centriole, no giant centrospheres could be found. Occasionally, however, in cells that had taken in pigment liberated by the death of the tumor cells, these structures could be seen.

In the giant-cell tumors no giant centrospheres or foam cells could be seen. In every one of these cases the growth appeared to be active and healthy and resembled very closely that seen in the eight xanthomata which did not contain giant centrospheres or foam cells. The types of cells containing the pigment in the giant-cell tumors of bone appear to be identical with those that contain the pigment in the xanthomatous tumors, and one would therefore expect to find giant centrospheres in this class of tumors also, if the growth of the tumor became arrested and degeneration began. No evidence of either giant centrospheres or foam cells was found in the bone sarcomata.

Dr. W. H. Lewis, in his study of the giant centrosphere in tissue cultures, has shown that the so-called Plimmer body (cancer-cell inclusions, bird's-eye inclusions, etc.) and the giant centrosphere are identical. He points out that the presence of the giant centrosphere is evidence of disturbance in the metabolism of the cell and suggests that these bodies might be found in pathological conditions other than cancer. This prediction has been fulfilled in part by the discovery of the giant centrosphere in xanthomatous tumors.

It should be remembered that this discovery was purely an accident. If these cells had not contained pigment granules forming a corona about the giant centrosphere, this body would never have been observed in sections prepared according to our routine pathological technique. This suggests that, with more refined cytological methods, definite alterations in the cells might be found in a number of abnormal conditions which are now considered as functional because they show no definite pathological changes with the usual technique.

SUMMARY

Giant centrospheres were present in the pigment-containing cells of nine out of seventeen xanthomatous

tumors examined. They are probably to be regarded as evidence of degeneration.

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EXPLANATION OF FIGURES

FIG. 1.—Photomicrograph of a xanthoma (Surg. Path. No. 3890) which shows that a large number of the cells are filled with pigment granules. Some of the cells appear as circumscribed black splotches in which no details can be distinguished. In some of the others can be seen the clear central area which is the giant centrosphere. One cell, which is seen to the right and a little below the center, shows both nucleus and giant centrosphere, the latter surrounded by a corona of granules. (X 480.)

FIG. 2.—Camera-lucida drawing of a cell containing pigment granules and a few adjacent nuclei from the same section as Fig. 1. The nucleus appears somewhat swollen and the outlines of the cytoplasm are indicated merely by the extent of the granules. The giant centrosphere occupies the center of the cell and displaces the nucleus to one side. The granules are collected about the centrosphere except where it comes in direct contact with the nucleus. (X 2600.)

FIG. 3.—Another cell, showing a younger stage in the accumulation of granules from the same section. The nucleus is swollen and the pigment granules are massed at one end of it, probably around a centriole. There is no evidence of a centrosphere. (X 2600.)

A NORMAL PREGNANCY FOLLOWING INSERTION OF THE OUTER HALF OF A FALLOPIAN TUBE INTO THE UTERINE CORNU

By THOMAS S. CULLEN

In the Johns Hopkins Hospital Bulletin for September, 1921, Dr. Henry N. Shaw reported the case of a patient upon whom I had operated on Oct. 6, 1919. Her right tube and ovary had been removed by another surgeon several years before.

She entered the Johns Hopkins Hospital with signs of a left tubal pregnancy. On opening the abdomen I found a left cornual pregnancy. This was removed but the outer half of the left tube was saved, and its inner end was sutured into the uterine cornu.

She subsequently became pregnant but lost her baby on March 11, 1921, at the end of the seventh month. There was a placenta prævia.

On June 26, 1922 I received the following letter from Andrews, S. C. "Mrs. J. R. L. asked me to write you that she gave birth to a seven and a half pound baby girl this morning at eight-thirty. Dr. D. S. Porter was with her, labor was perfectly normal, both mother and child are doing finely so far."

Those who use every effort to save the tubes and ovaries or part of them will from time to time be disappointed and may be forced to do a second operation. The results in this case, on the other hand, clearly demonstrate what may occasionally be accomplished by judicious conservatism.

AN OPERATION FOR THE TOTAL EXTIRPATION OF TUMORS IN THE CEREBELLO-PONTINE ANGLE. A PRELIMINARY REPORT

By DR. WALTER E. DANDY

The most frequent tumor in the cerebello-pontine angle is an encapsulated endothelioma arising from the leptomeninges. Rather loosely embedded in the lateral wall of the brain-stem, it is potentially a benign tumor by virtue of its encapsulation. Its complete removal offers a permanent cure to the afflicted individual but its extirpation has been attended by a mortality so high as to render such attempts inadvisable. In fact, the complete removal of such tumors with recovery has been regarded as impossible. As a result, a partial intracapsular enucleation has been the operation which has seemed to offer most to the patient, but it is obvious that such treatment of a potentially benign lesion is most unsatisfactory to the patient, for the tumor must inevitably recur.

Five years ago, I completely removed such a growth from a patient who has since remained well. The growth was extirpated *in toto* by careful dissection around the tumor. Subsequently, two other tumors of the same type were similarly removed, but the results of such a method were too capricious and the mortality was too high.

Gradually a procedure has been evolved by which I believe these neoplasms can be successfully removed and with relative safety; the mortality should be little higher than from a subtotal removal of the contents of the tumor. The last two patients with cerebello-pontine tumors have been treated by this procedure and are well. The last

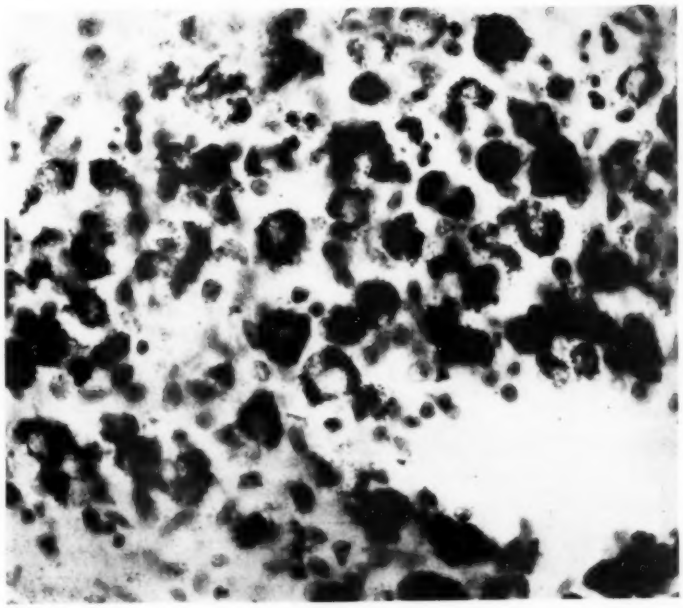

FIG. 1.

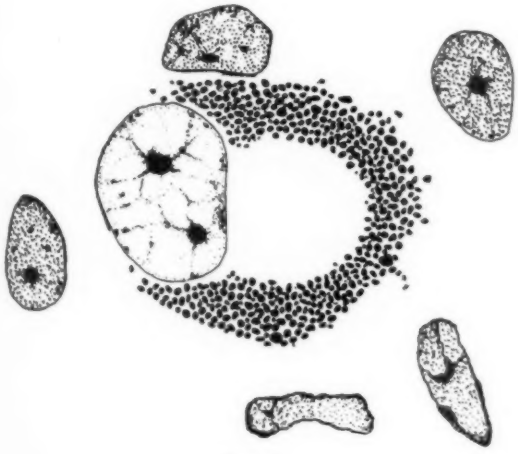

FIG. 2.

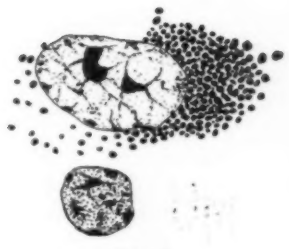

FIG. 3.

patient was a particularly bad risk because of a partial hemiplegia and hemianæsthesia and inability to swallow. She quickly recovered from the operation. In one patient, the operation was performed in two stages; in the second in one stage. The latter method is far preferable because in the interim between stages the capsule becomes friable and more difficult to handle.

The purpose of this preliminary report is to present the salient features of the operative procedure. A bilateral suboccipital exposure of the cerebellum is performed with as much exposure of the affected angle as possible. The interior of the growth is removed with a curette. Following this, the capsule is picked up with forceps and beginning at the upper and lower poles, carefully drawn away from the medulla, pons and mid-brain. The traction brings into view the several small veins and arteries crossing from the brain-stem to the tumor. These vessels are ligated individually with silver clips or fine silk ligatures and divided. Gradually, in this painstaking way, the whole tumor is delivered from its bed without bleeding, and without trauma to the brain-stem. The cranial nerves stretched by the tumor are automatically liberated as the capsule falls away from them.

NOTES ON NEW BOOKS

Human Embryology and Morphology. By ARTHUR KEITH. 4th Edition. Cloth, $10.50. (*New York, Longmans, Green & Co.: London: Edward Arnold, 1921.*)

In the fourth edition of his Human Embryology and Morphology, Sir Arthur Keith has emphasized the importance of studying the development of the human fetus in relation to the general facts of comparative anatomy and evolutionary history. This unique approach is essentially characteristic of the broad conceptions of the author and is most important because morphological embryology of today must assist in unravelling the problems of phylogeny and growth, or remain relatively sterile. The presentation is clear and excellent throughout and furnishes a particularly appropriate introduction to the study of both human and comparative anatomy. The numerous views which have been advanced regarding many phases of embryology have evidently been searchingly analysed and no criticism can be made of those that the author accepts. But these views have been presented as final and in this the book fails to meet one of the most important requirements of a modern text-book. The student should be given every opportunity of deciding for himself in regard to opposing theories and should not be taught, too finally, any individual theory as established truth. With the addition of a few pages devoted to the presentation of both sides of certain disputed points, this book would have stood alone as embodying the two most important requirements of a text-book: a fundamental and inspiring viewpoint, and a presentation sufficiently broad to bring the student face to face with the problems of a growing science.

R. S. C.

Arterial Sclerosis. By LOUIS FAUGERES BISHOP. (*London: Henry Frowde; Hodder & Stoughton, 1921.*)

It is greatly to be deplored that, in the making of books of which there is no end, a more critical judgment should not be exercised in determining not only the value of the content but the length of many of the volumes that are offered to an ever credulous public with the stamp of approval conveyed by the publisher's imprint.

It is difficult to understand why there should be, apparently, so great a popular demand for a work of the type of this volume, as to necessitate a third printing, that adds nothing of constructive value to our knowledge of arteriosclerosis. The work is an extraordinary mixture of the personal experiences and opinions of the author together with many excerpts from the writings of others, the whole being combined in such a way as to lead often to much confusion in the interpretation of the text. In his preface the author states that "clinical medicine either in the hands of reputable or disreputable practitioners is always anticipating the advance of knowledge," and further "the needs of physicians who have been trained in other specialties have been kept in mind and simplicity has been chosen rather than complexity."

In discussing the relationship of arteriosclerosis to blood pressure it is difficult to follow the author's apparent meaning. We disagree with the statement that "low blood pressure in arteriosclerosis may be regarded as an exception that always demands explanation." The following sentence quoted in full will illustrate our difficulty in interpreting the text—"The term blood pressure is often used where high blood pressure is meant. With light thrown on the meaning of the context this does not lead to confusion, though, of course, during life there is always pressure of blood in the vessels." (Chapter VI, p. 65, line 6 from top.)

We confess that we need light on "the context" and admit being led to confusion. We must, however, leave to his readers the ultimate decision as to the author's success in respect to the simplicity of his text.

The causes of arteriosclerosis discussed in a chapter of 16 pages contains not a single reference to the vast and fundamentally important literature upon the subject. The chapter entitled "The Natural History of Arteriosclerosis" following directly that devoted to the etiology, should be properly considered as a part of the former. Here again we have no reference to the literature and a delightful preliminary allusion to the life history of the oyster is followed by a most confused and inconsequential discussion of the subject. That the causes of arteriosclerosis are chemical and physical is a patent truism, but that the evolution of the disease process would in any large number of cases fall in with any such standard type as outlined on page 41, we seriously question. Great stress is laid upon high blood pressure apparently as evidenced by the systolic level, with but infrequent reference to the significance of the diastolic figures.

The chapter devoted to diet in arteriosclerosis and that upon the chemistry of the proteins should be read to be appreciated. The latter has at least the great merit of representing the statements of workers in this field from whose writings this chapter is largely constructed.

The essential purpose of the volume is apparently an exposition of the author's theories of the causal relationship between protein food intoxication and pathological cardiovascular changes, as well as his methods of therapeutic procedure in arteriosclerosis.

E. P. C.

Clinical Electrocardiography. By FREDERICK A. WILLIUS. Cloth, $5.00. (*Philadelphia and London, W. B. Saunders Company, 1922.*)

This volume covers in an elementary way the fundamental principles of the physiology of the galvanometer in its adaptation to clinical use, together with a short chapter on the mathematics in-

volved, and brief statements of the mechanism concerned with the various cardiac arrhythmias.

During the past two years a number of similar works have appeared each dealing with the subject in a way peculiar to the individual author. It is, however, very doubtful that any genuinely new knowledge has been contributed through these sources or even that the debatable points involved have been in any sense cleared up.

In a work intended primarily as an introduction to the subject, one would wish that dogma might be less emphatic and that a more conservative judgment as to the conclusions arrived at from the interpretation of the galvanometric records might obtain.

Although it is quite correct to say that a negative "P" wave may indicate a shift in the pace-maker, such a statement unqualified may easily lead to confusion and convey a false impression. In Chapter X dealing with the abnormalities of the "P" wave, this earlier impression is in a measure corrected, though it is greatly to be desired that the text devoted to this phase of the subject be revised.

Paroxysmal tachycardia is dealt with in a little over a page and there is no adequate discussion of sinus tachycardia in relation to what the author calls paroxysmal sinus tachycardia and paroxysmal auricular tachycardia. Are we to accept a paroxysmal tachycardia of sinus origin as proven, and is the term paroxysmal auricular tachycardia to be used to connote the presence of an ectopic and heterogenetic rhythm with negative "P" waves in all three derivations? Unless we consent to this view it is, of course, incorrect to say that the "P" wave is always inverted in paroxysmal tachycardia auricular in origin (p. 79). In the references to the literature following the chapter devoted to the auricular tachycardias there is no reference to Bouveret's original article which even to-day should be read by every student interested in this subject.

In the discussion of auricular fibrillation, although the present interpretation of its mechanism based upon the work of Lewis and his co-workers is referred to, no allusion is made to the development of localised areas of block, which is the underlying fault leading to the condition of fibrillation and really distinguishing it from flutter, and no reference in this connection is made to the fundamental work of Meyer, Mines and Garrey.

In the light of our knowledge of the pathological physiology of flutter it is not correct to imply that the "P" wave is always inverted. While in some instances the "P" wave appears as a distinctly negative wave, in the vast majority of flutter records it can be read only as a diphasic curve (See Figs. 52 to 58), a fact which gives rise to the striking similarity seen from case to case, the only clinical condition of which this can be said to be true. The character of the "P" wave in the presence of a circus movement within the auricle must depend upon the relationship of the direction of the spread of the wave to the plane of the given derivation.

In discussing the subject of notched QRS complexes (p. 109) no allusion is made to the variation in these deformities which may occur under change of position and forced respiration seen so conspicuously in many instances, and depending upon the relationship of the plane of the derivation concerned to the direction of the axial spread of the excitation wave. To base sweeping conclusions upon notching of this complex in any statistical relationship to the clinical diagnosis without first determining their variability, seems to us wholly unwarranted.

The chapter devoted to the abnormalities of the "P" wave is based upon a purely theoretical conception of the author without any adequate proof and cannot fail to confuse and mislead the reader who has no fundamental knowledge of the subject. Such an attempt to elucidate the mystery of the "T" wave can serve no genuinely useful purpose and the effort to classify clinical-pathological states on the basis of the negativity of the "T" wave in any combination of derivations is too absurd to merit discussion.

The history of the development of our knowledge following the introduction of the galvanometer as an instrument for the study of clinical cases is the story of a brilliant and extraordinary insight into more than one obscure corner of medical science; its use, however, as suggested by the figures from pages 163-193 of this volume can only give the uninitiated an utterly false conception of the usefulness of the instrument in clinical procedure.

E. P. C.

Textbook of Physiology. By RUSSELL BURTON-OPITZ. (*Philadelphia and London: W. B. Saunders Co., 1920.*)

The author's aim, as he states it, is to supply the medical student with a text-book in the subject of human physiology. As such, as far as it goes, the book accomplishes its end in a satisfactory way. Physiology covers a vast field and the making of a book of this kind is no light task. The number of subjects are too many to be fully understood by any one man. Hence, that the product of the author's labor should contain errors was inevitable. Some of these will gradually get corrected in the newer editions. But the fact that older authors do not succeed altogether in this leads us to be not too sanguine. To illustrate my point I need only refer to the figure on p. 147 of the present book, showing the distribution of electrotonus along a nerve. The figure is Pflüger's down to the last detail of symbol and character of type, and the explanatory note below the figure is a free translation of Pflüger's explanatory note buried in the text of his monograph. For these facts the reader need only to turn to Figure 18, Plate V and p. 465 of the original. Yet not only does Burton-Opitz ascribe the diagram to American authorship but that master of text-books in Physiology, Professor Howell, chronically persists in doing likewise (see his 8th Edition). The error is clearly one of misapprehension or of oversight, and will persist, I presume, to the stroke of doom. In Burton-Opitz's book there is another figure, an original one—which clearly shows that here the author is describing something he does not well understand. The text describing the figure bears this out. I refer to the description of the principle, and application in physiology, of a thermopile, given on page 97. The thing is a failure. When the author touches topics nearer his own fields of research one at once perceives the note of authority, and it is in these parts on the blood and circulation that the book has especial merit. Now this unevenness in text-book writing suggests that it is high time that physiology as a text for the student should no longer be written by one man. It has been suggested that, to avoid the difficulty of getting a dozen specialists to co-operate on one book, the subject could be satisfactorily covered by a dozen small treatises or special chapters separately printed. These could be revised and reprinted independently of each other and even by new authors as the older ones dropped the task. The convenience of handling and carrying the smaller volume need not be dwelt upon. Let us hope that the day of the cumbersome text-book is nearly ended.

C. D. S.

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